```
Welcome to DIALOG

Dialog level 05.22.00D
? b 411;set files biotech
     10nov08 09:46:50 User219511 Session D743.2
        $0.00   0.117 DialUnits File410
    $0.00  Estimated cost File410
    $0.19  TELNET
    $0.19  Estimated cost this search
    $0.76  Estimated total session cost   0.275 DialUnits
File 411:DIALINDEX(R)

DIALINDEX(R)
  (c) 2008 Dialog

*** DIALINDEX search results display in an abbreviated ***
*** format unless you enter the SET DETAIL ON command. ***
  You have 27 files in your file list.
  (To see banners, use SHOW FILES command)
? s SMAD1 and (sclerosis or (extracellular (w) matrix) or (IV and collagen))

Your SELECT statement is:
  s SMAD1 and (sclerosis or (extracellular (w) matrix) or (IV and
collagen))

        Items   File
        -----   ----
           24    5: Biosis Previews(R)_1926-2008/Oct W4
            4    8: EI Compendex(R)_1884-2008/Oct W4
            9   24: CSA Life Sciences Abstracts_1966-2008/Nov
           36   34: SciSearch(R) Cited Ref Sci_1990-2008/Nov W2
            8   45: EMCare_2008/Oct W4
           22   71: ELSEVIER BIOBASE_1994-2008/Oct W4
           27   72: EMBASE_1993-2008/Nov 10
           27   73: EMBASE_1974-2008/Nov 10
            1   98: General Sci Abs_1984-2008/Sep
           52  135: NewsRx Weekly Reports_1995-2008/Oct W4
            2  143: Biol. & Agric. Index_1983-2008/Aug
            6  144: Pascal_1973-2008/Nov W1
           29  154: MEDLINE(R)_1990-2008/Nov 06
           29  155: MEDLINE(R)_1950-2008/Nov 07
            2  172: EMBASE Alert_2008/Nov 05
            2  266: FEDRIP_2008/Aug
           11  399: CA SEARCH(R)_1967-2008/UD=14920

  17 files have one or more items; file list includes 27 files.

? save temp; b 154,155,5,71,72,73,399,exs;rd
Temp SearchSave "TH623788178" stored
     10nov08 09:48:55 User219511 Session D743.3
        $3.35   1.140 DialUnits File411
    $3.35  Estimated cost File411
    $0.80  TELNET
    $4.15  Estimated cost this search
    $4.91  Estimated total session cost   1.415 DialUnits

SYSTEM:OS - DIALOG OneSearch
  File 154:MEDLINE(R) 1990-2008/Nov 06
       (c) format only 2008 Dialog
  File 155:MEDLINE(R) 1950-2008/Nov 07
       (c) format only 2008 Dialog
  File   5:Biosis Previews(R) 1926-2008/Oct W4
       (c) 2008 The Thomson Corporation
  File  71:ELSEVIER BIOBASE 1994-2008/Oct W4
       (c) 2008 Elsevier B.V.
  File  72:EMBASE 1993-2008/Nov 10
       (c) 2008 Elsevier B.V.
  File  73:EMBASE 1974-2008/Nov 10
       (c) 2008 Elsevier B.V.
  File 399:CA SEARCH(R) 1967-2008/UD=14920
       (c) 2008 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
IPCR/8 classification codes now searchable as IC=. See HELP NEWSIPCR.

    Set  Items  Description
    ---  -----  -----------
Executing TH623788178
        4402  SMAD1
      374441  SCLEROSIS
     1066190  EXTRACELLULAR
     1085053  MATRIX
      306280  EXTRACELLULAR(W)MATRIX
     1285251  IV
      584777  COLLAGEN
 S1     169  SMAD1 AND (SCLEROSIS OR (EXTRACELLULAR (W) MATRIX) OR (IV
             AND COLLAGEN))
 S2      62  RD  (unique items)
? t s2/7/1-62;bye

 2/7/1     (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

28079474  PMID: 18434745
  Altered transforming growth factor-beta signaling in a murine model of
thoracic aortic aneurysm.
  Jones Jeffrey A; Barbour John R; Stroud Robert E; Bouges Shenikqua;
Stephens Shelly L; Spinale Francis G; Ikonomidis John S
  Department of Surgery, Division of Cardiothoracic Surgery Research,
Medical University of South Carolina, Ralph H. Johnson Veterans Affairs
Medical Center, Charleston, SC 29425, USA. jonesja@musc.edu
  Journal of vascular research (Switzerland)  2008, 45 (6) p457-68.
ISSN 1423-0135--Electronic  Journal Code: 9206092
  Contract/Grant No.: HL059165-07; HL; United States NHLBI; R01 HL075488-04
; HL; United States NHLBI
  Publishing Model Print-Electronic
  Document type: Journal Article; Research Support, N.I.H., Extramural;
Research Support, U.S. Gov't, Non-P.H.S.
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: MEDLINE; Completed
  OBJECTIVE: Thoracic aortic aneurysms (TAAs) develop by a multifactorial
process involving maladaptive signaling pathways that alter the aortic
vascular environment. Transforming growth factor-beta (TGF-beta) has been
implicated in regulating the structure and composition of the
%%%extracellular%%% %%%matrix%%% by differential activation of various
intracellular signaling pathways. However, whether and to what degree
TGF-beta signaling contributes to TAA development remains unclear.
Accordingly, the hypothesis that alterations in TGF-beta signaling occur
during aneurysm formation was tested in a murine model of TAA. METHODS:
TAAs were surgically induced in mice (C57BL/6J) and aortas were analyzed at
predetermined time points (1, 2, and 4 weeks post-TAA induction).
Quantitative real-time PCR (QPCR) was performed to evaluate the expression
of 84 relevant TGF-beta superfamily genes, and the protein levels of key
signaling intermediates were measured by immunoblotting. Results were
compared to unoperated reference control mice. RESULTS: QPCR revealed
increased expression of TGF-beta superfamily ligands (Gdf-2, -6, -7,
Inhba), ligand inhibitors (Bmper, Chrd, Gsc), and transcriptional
regulators (Dlx2, Evi1), among other genes (Colx2b, Igf1, IL-6). Protein
levels of TGF-beta receptor(II), Smad2, %%%Smad1%%%/5/8, phospho-
%%%Smad1%%% /5/8, and Smurf1 were increased from control values post-TAA
induction. Both TGF-beta receptor(I) and Smad4 were decreased from control
values, while ALK-1 levels remained unchanged. CONCLUSIONS: These
alterations in the TGF-beta pathway suggest a mechanism by which primary
signaling is switched from a TGF-betaR(I)/Smad2-dependent response, to an
ALK-1/%%%Smad1%%% /5/8 response, representing a significant change in
signaling outcome, which may enhance matrix degradation. Copyright 2008 S.
Karger AG, Basel
  Record Date Created: 20081021
  Record Date Completed: 20081106
```

Date of Electronic Publication. 20080423

2/7/2 (Item 2 from file. 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

27987204 PMID: 18923055
Podocyte-derived BMP7 is critical for nephron development.
Kazama Itsuro, Mahoney Zhen; Miner Jeffrey H; Graf Daniel; Economides Aris N, Kreidberg Jordan A
Division of Nephrology, Children's Hospital Boston, Harvard Medical School, Boston, MA 02115, USA.
Journal of the American Society of Nephrology - JASN (United States) Nov 2008, 19 (11) p2181-91, ISSN 1533-3450--Electronic Journal Code: 9013836
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Individuals with congenital renal hypoplasia display a defect in the growth of nephrons during development. Many genes that affect the initial induction of nephrons have been identified, but little is known about the regulation of postinductive stages of kidney development. In the absence of the growth factor bone morphogenic protein 7 (BMP7), kidney development arrests after induction of a small number of nephrons. The role of BMP7 after induction, however, has not been fully investigated. Here, we generated a podocyte-specific conditional knockout of BMP7 (Bmp7(flox/flox);Nphs2-Cre() [BMP7 CKO]) to study the role of podocyte-derived BMP7 in nephron maturation. By postnatal day 4, 65% of BMP7 CKO mice had hypoplastic kidneys, but glomeruli demonstrated normal patterns of laminin and %%%collagen%%% %%%IV%%% subunit expression. Developing proximal tubules, however, were reduced in number and demonstrated impaired cellular proliferation. We examined signaling pathways downstream of BMP7; the level of cortical phosphorylated %%%Smad1%%% , 5, and 8 was unchanged in BMP CKO kidneys, but phosphorylated p38 mitogen-activated protein kinase was significantly decreased. In addition, beta-catenin was reduced in BMP7 CKO kidneys, and its localization to intracellular vesicles suggested that it had been targeted for degradation. In summary, these results define a BMP7-mediated regulatory axis between glomeruli and proximal tubules during kidney development.
Record Date Created: 20081028
Date of Electronic Publication: 20081015

2/7/3 (Item 3 from file. 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

27958989 PMID: 18787191
BMPER is an endothelial cell regulator and controls bone morphogenetic protein-4-dependent angiogenesis.
Heinke Jennifer; Wehofsits Leonie; Zhou Qian; Zoeller Christoph; Baar Kim-Miriam; Helbing Thomas; Laib Anna, Augustin Hellmut; Bode Christoph; Patterson Cam; Moser Martin
Department of Cardiology, University of Freiburg, Germany.
Circulation research (United States) Oct 10 2008, 103 (8) p804-12, ISSN 1524-4571--Electronic Journal Code: 0047103
Publishing Model Print-Electronic
Document type: Journal Article, Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Bone morphogenetic proteins (BMPs) are involved in embryonic and adult blood vessel formation in health and disease. BMPER (BMP endothelial cell precursor-derived regulator) is a differentially expressed protein in embryonic endothelial precursor cells. In earlier work, we found that BMPER interacts with BMPs and when overexpressed antagonizes their function in embryonic axis formation. In contrast, in a BMPER-deficient zebrafish model, BMPER behaves as a BMP agonist. Furthermore, lack of BMPER induces a vascular phenotype in zebrafish that is driven by disarray of the intersomitic vasculature. Here, we investigate the impact of BMPER on endothelial cell function and signaling and elucidate its role in BMP-4 function in gain- and loss-of-function models. As shown by Western blotting and immunocytochemistry, BMPER is an %%%extracellular%%% %%%matrix%%% protein expressed by endothelial cells in skin, heart, and lung. We show that BMPER is a downstream target of FoxO3a and consistently exerts activating effects on endothelial cell sprouting and migration in vitro and in vivo. Accordingly, when BMPER is depleted from endothelial cells, sprouting is impaired. In terms of BMPER related intracellular signaling, we show that BMPER is permissive and necessary for Smad 1/5 phosphorylation and induces Erk1/2 activation. Most interestingly, BMPER is necessary for BMP-4 to exert its activating role in endothelial function and to induce Smad 1/5 activation. Vice versa, BMP-4 is necessary for BMPER activity. Taken together, BMPER is a dose-dependent endothelial cell activator that plays a unique and pivotal role in fine-tuning BMP activity in angiogenesis.
Record Date Created: 20081010
Record Date Completed: 20081023
Date of Electronic Publication: 20080911

2/7/4 (Item 4 from file. 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

27614002 PMID: 18668566
%%%Smad1%%% pathway is activated in systemic %%%sclerosis%%% fibroblasts and is targeted by imatinib mesylate.
Pannu Jaspreet; Asano Yoshihide; Nakerakanti Sashidhar; Smith Edwin; Jablonska Stefania; Blaszczyk Maria; ten Dijke Peter; Trojanowska Maria
Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, SC 29425-6370, USA.
Arthritis and rheumatism (United States) Aug 2008, 58 (8) p2528-37, ISSN 0004-3591--Print Journal Code: 0370605
Contract/Grant No.: AR 42334; AR; United States NIAMS; AR 44883; AR; United States NIAMS
Publishing Model Print; Comment in Arthritis Rheum. 2008 Aug;58(8):2219-24; Comment in PMID 18668575
Document type: Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: Activation of %%%Smad1%%% signaling has recently been implicated in the development of fibrosis. The goal of the present study was to gain further insights into activation of the %%%Smad1%%% pathway in fibrosis in systemic %%%sclerosis%%% (SSc) and to determine whether this pathway is targeted by the antifibrotic drug imatinib mesylate. METHODS: Levels of phosphorylated %%%Smad1%%% and total %%%Smad1%%% were examined in SSc and control skin biopsy samples by immunohistochemistry and in cultured fibroblasts by Western blotting. Activity of the CCN2 promoter was examined by a luciferase reporter gene assay. Interactions of %%%Smad1%%% with the CCN2 promoter were examined by in vitro and in vivo DNA binding assays. Expression of the nonreceptor tyrosine kinase c-Abl and %%%Smad1%%% was blocked using respective small interfering RNA. RESULTS: Total and phosphorylated %%%Smad1%%% levels were significantly elevated in SSc skin biopsy samples and in cultured SSc fibroblasts and correlated with elevated CCN2 protein and CCN2 promoter activity. DNA binding assays demonstrated that %%%Smad1%%% was a direct activator of the CCN2 gene. Small interfering RNA-mediated depletion of %%%Smad1%%% in SSc fibroblasts normalized the production of CCN2 and collagen. Imatinib mesylate blocked activation of the %%%Smad1%%% pathway in transforming growth factor beta-stimulated control fibroblasts and reversed activation of this pathway in SSc fibroblasts. Likewise, blockade of c-Abl abrogated activation of the %%%Smad1%%% pathway in SSc fibroblasts. CONCLUSION: Our findings demonstrate that activation of %%%Smad1%%% signaling occurs in a subset of

SSc patients and contributes to persistent activation of SSc fibroblasts. Demonstration that the %%%Smad1%%% /CCN2 pathway is blocked by imatinib mesylate further clarifies the mechanism of the antifibrotic effects of this compound. This study suggests that SSc patients with activated %%%Smad1%%% signaling may benefit from imatinib mesylate treatment.
Record Date Created: 20080807
Record Date Completed: 20080918

2/7/5 (Item 5 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

27336733 PMID: 18333754
ALK1 opposes ALK5/Smad3 signaling and expression of %%%extracellular%%% %%%matrix%%% components in human chondrocytes.
Finnson Kenneth W; Parker Wendy L; ten Dijke Peter; Thorikay Midory; Philip Anie
Division of Plastic Surgery, Department of Surgery, McGill University, Montreal, Quebec, Canada.
Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research (United States) Jun 2008, 23 (6) p896-906, ISSN 1523-4681--Electronic Journal Code: 8610640
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
INTRODUCTION: TGF-beta is a multifunctional regulator of chondrocyte proliferation, differentiation, and %%%extracellular%%% %%%matrix%%% production. Dysregulation of TGF-beta action has been implicated in cartilage diseases such as osteoarthritis. TGF-beta signaling is transduced through a pair of transmembrane serine/threonine kinases, known as the type I (ALK5) and type II receptors. However, recent studies on endothelial cells have identified ALK1 as a second type I TGF-beta receptor and have shown that ALK1 and ALK5 have opposing functions in these cells. Here we examined ALK1 expression and its regulation of TGF-beta signaling and responses in human chondrocytes. MATERIALS AND METHODS: ALK1 expression in human chondrocytes was examined by RT-PCR and Western blot. The ability of ALK1 to form complexes with other TGF-beta receptors was determined by affinity labeling/immunoprecipitation and by immunoprecipitation followed by Western blot. The effect of ALK1 on TGF-beta1-induced signaling and responses was determined by varying ALK1 expression levels and measuring transcriptional activity using promoter/luciferase assays, %%%Smad1%%%/5 and Smad3 phosphorylation, and expression of type II collagen, PAI-1, and fibronectin. RESULTS: Our results indicate that ALK1 is expressed in human chondrocytes and that it is a component of the TGF-beta receptor system, associating with ALK5, type II TGF-beta receptor, endoglin, and betaglycan. Furthermore, we show that both ALK1 and ALK5 are needed for TGF-beta-induced phosphorylation of intracellular mediators %%%Smad1%%%/5, whereas only ALK5 is essential for TGF-beta1-induced phosphorylation of Smad3. In addition, our results show that ALK1 inhibits, whereas ALK5 potentiates, TGF-beta-induced Smad3-driven transcriptional activity and the expression of PAI-1, fibronectin, and type II collagen in chondrocytes. CONCLUSIONS: Our results suggest that ALK1 and ALK5 display opposing functions in human chondrocytes, implicating an essential role for ALK1 in the regulation of TGF-beta signaling and function in these cells.
Record Date Created: 20080618
Record Date Completed: 20080812

2/7/6 (Item 6 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

27022116 PMID: 17967138
Murnine and chicken chondrocytes regulate osteoclastogenesis by producing RANKL in response to BMP2.
Usui Michihiko; Xing Lianping; Drissi Hicham; Zuscik Michael; O'Keefe Regis; Chen Di; Boyce Brendan F
Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, New York 14642, USA.
Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research (United States) Mar 2008, 23 (3) p314-25, ISSN 1523-4681--Electronic Journal Code: 8610640
Contract/Grant No.: AR 48697; AR; United States NIAMS, AR43510; AR; United States NIAMS; AR49305; AR; United States NIAMS
Publishing Model Print
Document type: Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Chondrocytes express RANKL, but their role in osteoclastogenesis is not clear. We report that hypertrophic chondrocytes induce osteoclast formation through RANKL production stimulated by BMP2 and Runx2/%%%Smad1%%% and thus they may regulate resorption of calcified matrix by osteoclasts at growth plates. INTRODUCTION: Bone morphogenetic protein (BMP) signaling and Runx2 regulate chondrogenesis during bone development and fracture repair and RANKL expression by osteoblaststromal cells. Chondrocytes express RANKL, and this expression is stimulated by vitamin D3, but it is not known if chondrocytes directly support osteoclast formation or if BMPs or Runx2 is involved in this potential regulation of osteoclastogenesis. MATERIAL AND METHODS: The chondrocyte cell line, ATDC5, primary mouse sternal chondrocytes, and chick sternal chondrocytes were used. Cells were treated with BMP2, and expression of RANKL and chondrocyte marker genes was determined by real-time RT-PCR and Western blot. Chondrocytes and spleen-derived osteoclast precursors BMP2 were co-cultured to examine the effect of chondrocyte-produced RANKL on osteoclast formation. A reporter assay was used to determine whether BMP2-induced RANKL production is through transcriptional regulation of the RANKL promoter and whether it is mediated by Runx2. RESULTS: BMP2 significantly increased expression of RANKL mRNA and protein in all three types of chondrocytes, particularly by Col X-expressing and upper sternal chondrocytes. Chondrocytes constitutively induced osteoclast formation. This effect was increased significantly by BMP2 and prevented by RANK:Fc. BMP2 significantly increased luciferase activity of the RANKL-luc reporter, and %%%Smad1%%% increased this effect. Deletion or mutation of Runx2 binding sites within the RANKL promoter or overexpression of a dominant negative Runx2 abolished BMP2- and %%%Smad1%%%-mediated activation of RANKL promoter activity. CONCLUSIONS: Hypertrophic chondrocytes may regulate osteoclastogenesis at growth plates to remove calcified matrix through BMP-induced RANKL expression.
Record Date Created: 20080227
Record Date Completed: 20080624

2/7/7 (Item 7 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

25451717 PMID: 17967875
Conditional deletion of %%%Smad1%%% and Smad5 in somatic cells of male and female gonads leads to metastatic tumor development in mice.
Pangas Stephanie A; Li Xiaohui; Umans Lieve; Zwijsen An; Huylebroeck Danny; Gutierrez Carolina; Wang Degang; Martin James F; Jamin Soazik P; Behringer Richard R; Robertson Elizabeth J; Matzuk Martin M
Department of Pathology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA. spangas@bcm.edu
Molecular and cellular biology (United States) Jan 2008, 28 (1) p248-57, ISSN 1098-5549--Electronic Journal Code: 8109087
Contract/Grant No.: 5F32HD46335; HD; United States NICHD; HD12324, HD; United States NICHD; HD30284; HD; United States NICHD, HD32067; HD; United States NICHD; HD44156; HD; United States NICHD
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The transforming growth factor beta (TGFbeta) family has critical roles in the regulation of fertility. In addition, the pathogenesis of some human cancers is attributed to misregulation of TGFbeta function and SMAD2 or SMAD4 mutations. There are limited mouse models for the BMP signaling SMADs (BR-SMADs) 1, 5, and 8 because of embryonic lethality and suspected genetic redundancy. Using tissue-specific ablation in mice, we deleted the BR-SMADs from somatic cells of ovaries and testes. Single conditional knockouts for %%%Smad1%%% or Smad5 or mice homozygous null for Smad8 are viable and fertile. Female double %%%Smad1%%% Smad5 and triple %%%Smad1%%% Smad5 Smad8 conditional knockout mice become infertile and develop metastatic granulosa cell tumors. Male double %%%Smad1%%% Smad5 conditional knockout mice are fertile but demonstrate metastatic testicular tumor development. Microarray analyses indicated significant alterations in expression of genes related to the TGFbeta pathway, as well as genes involved in infertility and %%%extracellular%%% %%%matrix%%% production. These data strongly implicate the BR-SMADs as part of a critical developmental pathway in ovaries and testis that, when disrupted, leads to malignant transformation.
Record Date Created: 20071219
Record Date Completed: 20080111
Date of Electronic Publication: 20071029

2/7/8 (Item 8 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

25064399 PMID: 17670744
Matrix GLA protein, an inhibitory morphogen in pulmonary vascular development.
Yao Yucheng; Nowak Sarah; Yochelis Arik; Garfinkel Alan; Bostrom Kristina I
Division of Cardiology, David Geffen School of Medicine, UCLA, Los Angeles, California 90095-1679.
Journal of biological chemistry (United States) Oct 12 2007, 282 (41) p30131-42. ISSN 0021-9258--Print Journal Code: 2985121R
Contract/Grant No.: HL30568; HL; United States NHLBI; HL78931; HL; United States NHLBI; HL81397; HL; United States NHLBI
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
Deficiency of matrix GLA protein (MGP), an inhibitor of bone morphogenetic protein (BMP)-2/4, is known to cause arterial calcification and peripheral pulmonary artery stenosis. Yet the vascular role of MGP remains poorly understood. To further investigate MGP, we created a new MGP transgenic mouse model with high expression of the transgene in the lungs. The excess MGP led to a disruption of the pulmonary pattern of BMP-4, and resulted in significant morphological defects in the pulmonary artery tree. Specifically, the vascular branching pattern lacked characteristic side branching, whereas control lungs had extensive side branching accounting for as much as 40% of the vascular endothelium. The vascular changes could be explained by a dramatic reduction of phosphorylated %%%SMAD1%%%/5/8 in the alveolar epithelium, and in epithelial expression of the activin-like kinase receptor 1 and vascular endothelial growth factor, both critical in vascular formation. Abnormalities were also found in the terminal airways and in lung cell differentiation; high levels of surfactant protein-B were distributed in an abnormal pattern suggesting lost coordination between vasculature and airways. Ex vivo, lung cells from MGP transgenic mice showed higher proliferation, in particular surfactant protein B-expressing cells, and conditioned medium from these cells poorly supported in vitro angiogenesis compared with normal lung cells. The vascular branching defect can be mechanistically explained by a computational model based on activator/inhibitor reaction-diffusion dynamics, where BMP-4 and MGP are considered as an activating and inhibitory morphogen, respectively, suggesting that morphogen interactions are important for vascular branching.
Record Date Created: 20071008
Record Date Completed: 20071127
Date of Electronic Publication: 20070801

2/7/9 (Item 9 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

17782039 PMID: 17638757
In vitro effects of combined and sequential bone morphogenetic protein administration.
Arosarena Oneida A; Puleo David
Department of Otolaryngology, Temple University School of Medicine, 3400 N Broad St, Kresge Hall, Ste 102, Philadelphia, PA 19140, USA. oneida.arosarena@temple.edu
Archives of facial plastic surgery : official publication for the American Academy of Facial Plastic and Reconstructive Surgery, Inc. and the International Federation of Facial Plastic Surgery Societies (United States) Jul-Aug 2007, 9 (4) p242-7, ISSN 1521-2491--Print Journal Code: 100883500
Contract/Grant No.: AR048700; AR; United States NIAMS; EB02958; EB; United States NIBIB
Publishing Model Print
Document type: In Vitro; Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
OBJECTIVE: To assess the effects of combined and sequential administration of bone morphogenetic protein 2 (BMP-2) and BMP-7 on osteoblastic differentiation compared with administration of single growth factors. DESIGN: In vitro study of osseous differentiation in murine pluripotent cells using assays of %%%extracellular%%% %%%matrix%%% calcification, alkaline phosphatase activity, and expression of osseous markers. Mesenchymal cells were cultured with BMP-2, BMP-7, or a combination of these growth factors or were sequentially exposed to the growth factors. RESULTS: Sequential administration of BMP-2 and BMP-7 resulted in increased %%%extracellular%%% %%%matrix%%% calcification and expression of osteocalcin, whereas all groups treated with BMP up-regulated expression of the osteoblastic transcription factor Runx2/cbfa1, type I collagen, and the inhibitory BMP second messenger Smad6. None of the experimental groups demonstrated increased expression of osteopontin or %%%Smad1%%%, and only cells treated with concurrent administration of BMP-2 and BMP-7 increased Smad5 expression. Alkaline phosphatase activity was increased from baseline only in cells treated with BMP-2 alone. CONCLUSIONS: Culture with BMP-2 and BMP-7, their sequential administration, and their coadministration had variable effects on osseous differentiation in mesenchymal cells. These results demonstrate the need for increased understanding of the role of growth factors and their combinations in bone development and have important implications for the ongoing development of osteoinductive therapies.
Record Date Created: 20070719
Record Date Completed: 20070906

2/7/10 (Item 10 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

17757708 PMID: 17455258
Induction of %%%Smad1%%% by MT1-MMP contributes to tumor growth.
Freudenberg Jaclyn A; Chen Wen-Tien
Department of Medicine, Stony Brook University, Stony Brook, NY 11794-8151, USA.
International journal of cancer. Journal international du cancer (United States) Sep 1 2007, 121 (5) p966-77, ISSN 0020-7136--Print Journal Code: 0042124
Contract/Grant No.: M01 RR010710-070061; RR; United States NCRR; R01 CA039077; CA; United States NCI; R01 CA039077-20; CA; United States NCI; R01 CA039077-21; CA; United States NCI; R01 CA039077-22; CA; United States NCI; R01 EB002065; EB; United States NIBIB; R01 EB002065-17; EB; United

States NIBIB, R01 EB002065-16, EB; United States NIBIB, R01 EB002065-19, EB , United States NIBIB, R01 EB002065-20, EB, United States NIBIB, R41 CA103467-01, CA, United States NCI
Publishing Model:Print
Document type: Journal Article, Research Support, N.I.H., Extramural
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
MT1-MMP is a key integral membrane protease, which regulates tumor growth by cleaving %%%extracellular%%% %%%matrix%%% components, activating growth factors and receptors, and consequently, triggering downstream signals. To study what genes or pathways are mediated by endogenous MT1-MMP during tumor growth in vivo, we stably suppressed endogenous MT1-MMP in human tumor cells using RNA interference (RNAi). Tumor growth was significantly reduced in tumors derived from MT1-MMP-suppressed cells relative to control cells; the effect was rescued in cells engineered to re-express MT1-MMP expression. Gene expression profiling of cultured and tumor-derived cells by DNA microarray and real-time RT-PCR revealed that %%%Smad1%%% expression was upregulated in MT1-MMP-expressing cells and rapidly growing tumors; this was confirmed in 4 additional tumor cell lines. Furthermore, tumor growth of MT1-MMP-expressing cells was reduced when %%%Smad1%%% was suppressed by RNAi. We also found that the active form, but not the latent form, of TGF-beta was capable in promoting %%%Smad1%%% expression and 3D cell proliferation in MT1-MMP-suppressed cells. In addition, a dominant-negative form of the TGF-beta Type II receptor reduced %%%Smad1%%% expression in MT1-MMP-expressing cells. Thus, we propose that MT1-MMP functions, in part, to promote tumor growth by inducing the expression of %%%Smad1%%% via TGF-beta signaling. (c) 2007 Wiley-Liss, Inc.
Record Date Created: 20070702
Record Date Completed: 20071004

2/7/11 (Item 11 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

17650419 PMID: 17326134
BMP and FGF regulatory pathways in semilunar valve precursor cells.
Zhao Bin; Etter Laura; Hinton Robert B; Benson D Woodrow
Division of Cardiology, MLC 7042, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 45229, USA.
Developmental dynamics : an official publication of the American Association of Anatomists (United States) Apr 2007, 236 (4) p971-80, ISSN 1058-8388--Print Journal Code: 9201922
Contract/Grant No.: HD43005; HD; United States NICHD; HL069712; HL; United States NHLBI; HL074728; HL; United States NHLBI; HL085122; HL; United States NHLBI
Publishing Model:Print
Document type: Journal Article, Research Support, N.I.H., Extramural
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
In the developing atrioventricular (AV) valve, limb bud, and somites, cartilage cell lineage differentiation is regulated by bone morphogenetic protein (BMP), while fibroblast growth factor (FGF) controls tendon cell fate. We observed aggrecan and sox9, characteristic of cartilage cell types, and scleraxis and tenascin, characteristic of tendon cell types, in developing avian semilunar valves. Addition of BMP4 to outflow tract (OFT) precursor cells of young (E4.5) but not older (E6) chick embryos activated %%%Smad1%%%/5/8 and induced sox9 and aggrecan expression, while FGF4 treatment increased phosphorylated MAPK (pERK) signaling and promoted expression of scleraxis and tenascin. These results identify BMP and FGF pathways that promote expression of cartilage- or tendon-like characteristics in semilunar valve precursor cells. In contrast to AV valve precursor cells, which diversify into leaflets (cartilage-like) or chordae tendineae (tendon-like), semilunar valve cells exhibit both cartilage- and tendon-like characteristics in the developing and mature valve cusp.
Record Date Created: 20070430
Record Date Completed: 20070730

2/7/12 (Item 12 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

17629140 PMID: 17127702
Adenovirus-mediated expression of BMP-7 suppresses the development of liver fibrosis in rats.
Kinoshita Kohji; Iimuro Yuji; Otogawa Kohji; Saika Shizuya, Inagaki Yutaka; Nakajima Yuji; Kawada Norifumi; Fujimoto Jiro, Friedman Scott L, Ikeda Kazuo
First Department of Surgery, Hyogo College of Medicine, Nishinomiya, Japan.
Gut (England) May 2007, 56 (5) p706-14, ISSN 0017-5749--Print Journal Code: 2985108R
Contract/Grant No.: DK56621; DK; United States NIDDK
Publishing Model:Print-Electronic
Document type: Journal Article; Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
BACKGROUND: Liver cirrhosis, which is caused by the accumulation of %%%extracellular%%% %%%matrix%%% materials, is a serious clinical problem that can progress to hepatic failure. Transforming growth factor-beta (TGFbeta) plays a pivotal role in %%%extracellular%%% %%%matrix%%% production, but bone morphogenetic protein (BMP)-7, a member of the TGFbeta superfamily, can antagonise the fibrogenic activity of TGFbeta. AIM: In this study, we examined whether adenovirus-mediated overexpression of BMP-7 (Ad-BMP-7) antagonised the effect of TGFbeta in vitro and in vivo. METHODS AND RESULTS: In primary cultured rat stellate cells and the LX-2 human stellate cell line, induction of BMP-7 by Ad-BMP-7 infection decreased the expression of collagen 1A2 mRNA and smooth muscle alpha-actin in the presence or absence of TGFbeta, via Smad 1/5/8 phosphorylation. BMP-7 triggered the mRNA expression of inhibitors of differentiation 2 (Id2) in LX-2. Although endogenous expression of BMP-7 was hardly detectable, %%%Smad1%%% and Id2 overexpression increased BMP-7 expression in LX-2. A liver fibrosis model was induced by the repetitive intraperitoneal injection of thioacetamide (200 mg/kg body weight) twice per week for up to 7 weeks. In rats administered Ad-BMP-7 via the tail vein, hydroxyproline content and the areas stained by Sirius red dye in the liver were significantly reduced compared to controls. Ad-Id2 also reduced fibrosis. CONCLUSION: These data demonstrate that BMP-7, Smad 1/5/8 and Ids interact to antagonise hepatic fibrogenesis.
Record Date Created: 20070418
Record Date Completed: 20070529
Date of Electronic Publication: 20061124

2/7/13 (Item 13 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

17601487 PMID: 17317656
Transforming growth factor-beta receptor type I-dependent fibrogenic gene program is mediated via activation of %%%Smad1%%% and ERK1/2 pathways.
Pannu Jaspreet; Nakerakanti Sashidhar; Smith Edwin, ten Dijke Peter; Trojanowska Maria
Division of Rheumatology and Immunology, Medical University of South Carolina, Charleston, South Carolina 29425, USA.
Journal of biological chemistry (United States) Apr 2007, 282 (14) p10405-13, ISSN 0021-9258--Print Journal Code: 2985121R
Contract/Grant No.: AR-42334; AR; United States NIAMS; AR-44883, AR, United States NIAMS
Publishing Model:Print-Electronic
Document type: Clinical Trial; Journal Article; Research Support, N.I.H., Extramural
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The transforming growth factor (TGF)-beta/Smad3 signaling pathway is considered a central mediator of pathological organ fibrosis; however, contribution of Smad2/3-independent TGF-beta signaling has not been fully explored. The present study utilized previously a described model of scleroderma (SSc) fibrosis based on forced expression of the TGF-betaRI (ALK5) (Pannu, J., Gardner, H., Shearstone, J. R., Smith, E., and Trojanowska, M. (2006) Arthritis Rheum. 54, 3011-3021). This study was aimed at determining the molecular mechanisms underlying the profibrotic program in this model. We demonstrate that the TGF-betaRI-dependent up-regulation of %%%collagen%%% and CCN2 (CTGF) does not involve Smad2/3 activation but is mediated by ALK1/%%%Smad1%%% and ERK1/2 pathways. The following findings support this conclusion. (i) Smad2 and -3 were not phosphorylated in response to TGF-betaRI. (ii) a TGF-betaRI mutant defective in Smad2/3 activation, ALK5(3A), potently stimulated %%%collagen%%% production. (iii) elevation of TGF-betaRI triggered sustained association of ALK5 with ALK1 and high levels of %%%Smad1%%% phosphorylation, (%%%iv%%%) blockade of %%%Smad1%%% via small interfering RNA abrogated %%%collagen%%% and CCN2 up-regulation in this model. (v) elevated TGF-betaRI led to a prolonged activation of ERK1/2. (vi) the pharmacologic inhibitor of ERK1/2 inhibited %%%Smad1%%% phosphorylation and abrogated profibrotic effects of elevated TGFbeta-RI. Additional experiments demonstrated that a GC-rich response element located -6 to -16 (upstream of the transcription start site) in the CCN2 promoter mediated %%%Smad1%%% -dependent increased promoter activity in this model. This element was shown previously to mediate up-regulation of the CCN2 promoter in SSc fibroblasts. In conclusion, this study defines a novel ALK1/ %%%Smad1%%% - and ERK1/2-dependent, Smad3-independent mode of TGF-beta signaling that may operate during chronic stages of fibrosis in SSc.
Record Date Created: 20070402
Record Date Completed: 20070606
Date of Electronic Publication: 20070215

2/7/14 (Item 14 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

17270625 PMID: 17008304
Mutations of TGFbeta signaling molecules in human disease.
Harradine Kelly A; Akhurst Rosemary J
Cancer Research Institute, Comprehensive Cancer Center, University of California, San Francisco, CA 94143, USA.
Annals of medicine (Sweden) 2006, 38 (6) p403-14, ISSN 0785-3890--Print Journal Code: 8906398
Contract/Grant No.: P01 AR050440; AR; United States NIAMS; R01 GM60514; GM; United States NIGMS; R01 HL078564; HL; United States NHLBI
Publishing Model Print; Erratum in Ann Med. 2007;39(1) 79
Document type: Journal Article, Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
The transforming growth factor beta (TGFbeta) signaling pathway regulates several biological processes including cellular proliferation, differentiation, apoptosis, migration, and %%%extracellular%%% %%%matrix%%% deposition. Ligand and receptor family members signal through two main Smad signaling branches, TGFbeta/activin to Smad2/3 (Sma and MAD-related proteins) and bone morphogenetic protein (BMP) to %%%Smad1%%%/5. At the molecular level, TGFbeta acts by modifying cytoskeletal organization and ultimately regulating expression of specific target genes. Germline disruption of TGFbeta signaling leads to several types of hereditary congenital malformation or dysfunction of the skeletal, muscular and/or cardiovascular systems, and to cancer predisposition syndromes. In this review, the molecular etiology of TGFbeta-associated disorders is examined, together with a discussion of clinical overlap between syndromes and possible biological explanations underlying the variable penetrance and expressivity of clinical characteristics. Increasing our understanding of the molecular etiology underlying genotype-phenotype correlations will ultimately provide a molecular-based approach that should result in better prognostic tools, smart therapeutics and individualized disease management, not only for these rare syndromes, but for more generalized disorders of the cardiovascular and musculoskeletal systems and cancer. The clinical consequence of TGFbeta signaling mutations appears to depend on environmental factors and on the basal levels of ongoing signaling transduction networks specific to each individual. In this respect, genetic background might be a central factor in determining disease outcome and treatment strategy for TGFbeta-associated diseases. (96 Refs.)
Record Date Created: 20060929
Record Date Completed: 20070130

2/7/15 (Item 15 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

17205320 PMID: 16767106
Angiotensin II-dependent Src and %%%Smad1%%% signaling pathway is crucial for the development of diabetic nephropathy.
Mima Akira; Matsubara Takeshi; Arai Hidenori; Abe Hideharu; Nagai Kojiro; Kanamori Hiroshi; Sumi Eriko; Takahashi Toshikazu; Iehara Noriyuki; Fukatsu Atsushi; Kita Toru; Doi Tochio
Department of Nephrology, Kyoto University Graduate School of Medicine, Kyoto, Japan.
Laboratory investigation; a journal of technical methods and pathology (United States) Sep 2006, 86 (9) p927-39, ISSN 0023-6837--Print Journal Code: 0376617
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Angiotensin II (Ang II) is known to play a pivotal role in the development of diabetic nephropathy. However, the precise mechanism of Ang II-mediated effects on diabetic nephropathy is still unknown. We have reported that %%%Smad1%%% plays a key role in diabetic mesangial matrix expansion and directly regulates the transcription of type %%%IV%%% %%%collagen%%% (Col4) in vitro and in vivo. Here we examined the effect of Ang II on the expression of %%%Smad1%%% and mesangial matrix expansion in streptozotocin (STZ)-induced diabetic rats in vivo, using Ang II type 1 receptor blocker, olmesartan. We also examined the signaling mechanism by which Ang II induces mesangial matrix expansion in vitro. Treatment of diabetic rats with low-dose olmesartan for 20 weeks reduced albuminuria and hyperfiltration without affecting blood pressure and inhibited mesangial matrix expansive changes and the expression of Col4 and smooth muscle alpha actin compared with those in untreated rats. Immunohistochemical staining and Western blotting showed that the increased expression of %%%Smad1%%%, phospho-%%%Smad1%%% , and phospho-Src was inhibited by olmesartan. Ang II induced Col4 synthesis and increased expression of phospho-Src and phospho-%%%Smad1%%% in cultured mesangial cells, which was blocked by olmesartan. PP2, a Src tyrosine kinase inhibitor, and overexpression of dominant negative Src also reduced the phosphorylation of %%%Smad1%%%. Moreover, addition of small-interfering RNA against Src significantly reduced the phosphorylation of %%%Smad1%%% and synthesis of Col4. Taken together, these results indicate that Ang II can regulate the development of mesangial matrix expansion in the early phase of diabetic nephropathy through Src and %%%Smad1%%%.
Record Date Created: 20060823
Record Date Completed: 20061027
Date of Electronic Publication: 20060612

2/7/16 (Item 16 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

16939758 PMID: 16482100
Expression of %%%Smad1%%% is directly associated with mesangial matrix expansion in rat diabetic nephropathy.
Matsubara Takeshi; Abe Hideharu; Arai Hidenori; Nagai Kojiro; Mima Akira; Kanamori Hiroshi; Sumi Eriko; Takahashi Toshikazu; Matsuura Motokazu,

Iehara Noriyuki, Fukatsu Atsushi, Kita Toru; Doi Toshio
Department of Nephrology, Kyoto University Graduate School of Medicine, Kyoto, Japan.
Laboratory investigation; a journal of technical methods and pathology (United States) Apr 2006, 86 (4) p357-68, ISSN 0023-6837--Print
Journal Code: 0376617
Publishing Model Print
Document type: Journal Article, Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
Diabetic nephropathy is the leading cause of end-stage renal disease, and glomerular mesangial matrix expansion is the hallmark in diabetic nephropathy. However, the precise mechanism for the development of mesangial matrix expansion has remained unknown. The key component involved in mesangial matrix expansion is type %%%IV%%% %%%collagen%%% (Col4). Recently, we have reported that %%%Smad1%%% transcriptionally regulates expression of Col4 under diabetic conditions in vitro. Here we show that this direct regulator of Col4 also plays a crucial role for mesangial matrix expansion in vivo. Streptozotocin-induced diabetic rats are the model of incipient diabetic nephropathy, and showed various levels of mesangial matrix expansion at 24 weeks. The glomerular expression of %%%Smad1%%% was significantly increased in diabetic rats with more mesangial matrix expansion by Western blot and immunohistochemical analysis. Furthermore, the glomerular expression of %%%Smad1%%% was closely correlated with the glomerular expression of Col4 and smooth muscle alpha actin (alpha-SMA), while albuminuria or glomerular filtration rate was not correlated with mesangial matrix expansion. We also found that urinary excretion of %%%Smad1%%% was closely associated with the severity of mesangial matrix expansion. In cultured mesangial cells expression of %%%Smad1%%% upregulated the transcriptional activity of key molecules in mesangial matrix expansion, such as Col4 and alpha-SMA. These data indicate the critical involvement of %%%Smad1%%% in mesangial matrix expansion in the early phase of diabetic nephropathy. Our data imply that urinary %%%Smad1%%% might be a representative diagnostic marker for mesangial matrix expansion in diabetic nephropathy.
Record Date Created: 20060323
Record Date Completed: 20060606

2/7/17 (Item 17 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

16897369 PMID: 16326713
%%%Extracellular%%% %%%matrix%%% -mediated signaling by dentin phosphophoryn involves activation of the Smad pathway independent of bone morphogenetic protein.
Jadlowiec Julie A; Zhang Xiaoyuan; Li Jinhua; Campbell Phil G; Sfeir Charles
Department of Oral Medicine and Pathology, School of Dental Medicine, University of Pittsburgh, 3501 Terrace Street, Pittsburgh, PA 15261, USA.
Journal of biological chemistry (United States) Mar 3 2006, 281 (9) p5341-7, ISSN 0021-9258--Print Journal Code: 2985121R
Contract/Grant No.: DE 016123-01; DE; United States NIDCR
Publishing Model Print-Electronic
Document type: Journal Article, Research Support, N.I.H., Extramural; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
Cells have ingenious mechanisms for interpreting complex signals from their external microenvironment. Previously, we have shown that phosphophoryn (PP) regulates the expression of bone/dentin marker genes via the integrin/MAPK signaling pathway (Jadlowiec, J., Koch, H., Zhang, X., Campbell, P. G., Seyedain, M., and Sfeir, C. (2004) J. Biol. Chem. 279, 53329-53330). We hypothesize that other signaling pathways important for mineralized tissue morphogenesis such as the Smad pathway could be involved in PP signaling. We determined activation of the Smad pathway in human adult mesenchymal stem cells following treatment with recombinant PP (rPP). We observed that PP enhanced phosphorylation of %%%Smad1%%% within 30 min and %%%Smad1%%% translocation to the nucleus within 1 h. PP up-regulated the expression of %%%Smad1%%% target genes, Smad6, Dlx5, and Runx2. The timing of PP activation of %%%Smad1%%% implies this is a direct effect, however, we also investigated the possible involvement of bone morphogenetic proteins in PP stimulation of the Smad pathway. PP was shown to up-regulate Bmp-2 gene expression 12 h post-treatment with PP, which is much later than initial detection of %%%Smad1%%% phosphorylation at 30 min. Furthermore, addition of Noggin did not block %%%Smad1%%% phosphorylation by PP. We propose that PP could signal via the Smad pathway by either directly stimulating the phosphorylation of %%%Smad1%%% via integrins or other mechanisms. These might include integrin/bone morphogenetic protein receptor interactions or involvement of PP with other growth factors leading to the modulation of intracellular signaling. It is noteworthy that a non-transforming growth factor-beta family member activates the Smad pathway. The role of PP in regulating the Smad pathway raises very interesting questions regarding the role of PP during bone and tooth development.
Record Date Created: 20060227
Record Date Completed: 20060523
Date of Electronic Publication: 20051202

2/7/18 (Item 18 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

16856354 PMID: 16226436
Heparan sulfate proteoglycans including syndecan-3 modulate BMP activity during limb cartilage differentiation.
Fisher Melanie C; Li Yingcui; Seghatoleslami M Reza; Dealy Caroline N; Kosher Robert A
Center for Regenerative Medicine and Skeletal Development, MC3705, Department of Oral Rehabilitation, Biomaterials, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06030, USA.
Matrix biology : journal of the International Society for Matrix Biology (Germany) Jan 2006, 25 (1) p27-39, ISSN 0945-053X--Print
Journal Code: 9432592
Contract/Grant No.: 5 T32 DE07302; DE; United States NIDCR; HD022610; HD; United States NICHD; HD041418; HD; United States NICHD
Publishing Model Print-Electronic
Document type: Journal Article, Research Support, N.I.H., Extramural
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
Bone morphogenetic proteins (BMPs) are involved in multiple aspects of limb development including regulation of cartilage differentiation. Several BMPs bind strongly to heparin, and heparan sulfate proteoglycans (HSPGs) at the cell surface or in the %%%extracellular%%% %%%matrix%%% have recently been implicated as modulators of BMP signaling in some developing systems. Here we have explored the role of HSPGs in regulating BMP activity during limb chondrogenesis by evaluating the effects of exogenous heparan sulfate (HS), heparitinase treatment, and overexpression of the HSPG syndecan-3 on the ability of BMP2 to modulate the chondrogenic differentiation of limb mesenchymal cells in micromass culture. Exogenous HS dramatically enhances the ability of BMP2 to stimulate chondrogenesis and cartilage specific gene expression, and reduces the concentration of BMP2 needed to stimulate chondrogenesis. Furthermore, HS stimulates BMP2-mediated phosphorylation of %%%Smad1%%%, Smad5, and Smad8, transcriptional mediators of BMP2 signaling, indicating that HS enhances the interaction of BMP2 with its receptors. Pretreatment of micromass cultures with heparitinase to degrade endogenous HSPGs also enhances the chondrogenic activity of BMP2, and reduces the concentration of BMP2 needed to promote chondrogenesis. Taken together these results indicate that exogenous HS or heparitinase enhance the chondrogenic activity of BMP2 by interfering with its interaction with endogenous HSPGs that would normally restrict its interaction with its receptors. Consistent with the possibility that HSPGs are negative modulators of BMP signaling during chondrogenesis, we have found that overexpression of syndecan-3, which is one of the major HSPGs normally expressed during chondrogenesis, greatly impairs the ablity of BMP2 to

promote cartilage differentiation. Furthermore, retroviral overexpression of syndecan-3 inhibits BMP2-mediated Smad phosphorylation in the regions of the cultures in which chondrogenesis is inhibited and in which ectopic syndecan-3 protein is highly expressed. These results indicate that syndecan-3 interferes with the interaction of BMP2 with its receptors, and that this interference results in an inhibition of chondrogenesis. Taken together these results indicate that HSPGs including syndecan-3 normally modulate the strength of BMP signaling during limb cartilage differentiation by limiting the effective concentration of BMP available for signaling.
Record Date Created: 20060130
Record Date Completed: 20060612
Date of Electronic Publication: 20051013

2/7/19 (Item 19 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

16847179 PMID: 16299553
The immunomodulator FTY720 and its phosphorylated derivative activate the Smad signalling cascade and upregulate connective tissue growth factor and %%%collagen%%% type %%%IV%%% expression in renal mesangial cells.
Xin Cuiyan; Ren Shuyu; Eberhardt Wolfgang; Pfeilschifter Josef; Huwiler Andrea
Pharmazentrum frankfurt Izafes, Klinikum der Johann Wolfgang Goethe-Universitat, Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany.
British journal of pharmacology (England) Jan 2006, 147 (2) p164-74, ISSN 0007-1188--Print Journal Code: 7502536
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
1.--The immunomodulating agent FTY720 is a substrate for the sphingosine kinase and the phosphorylated form is able to bind to sphingosine 1-phosphate (S1P) receptors. In this study, we show that exposure of renal mesangial cells to phospho-FTY720 leads to a rapid and transient activation of several protein kinase cascades, including the mitogen- and stress-activated protein kinases. The nonphosphorylated FTY720 also increased MAPK phosphorylation, but with a reduced potency and a more delayed time course. In addition, phospho-FTY720 and FTY720 are able to increase phosphorylation of Smad proteins which are classical members of the transforming growth factor-beta (TGF-beta) signalling device, thus suggesting a crosstalk between FTY720 and TGF-beta signalling. 2.--Pretreatment with the S1P(3) receptor antagonist suramin inhibits FTY720 and phospho-FTY720-induced Smad phosphorylation, whereas pertussis toxin pretreatment, which blocks G(i/0) proteins, has no effect on Smad phosphorylation. 3.--Since TGF-beta is a potent profibrotic cytokine in mesangial cells and upregulates the connective tissue growth factor (CTGF) and %%%collagen%%% as important hallmarks in the fibrotic sequelae, we investigated whether FTY720 and phospho-FTY720 are able to mimic these effects of TGF-beta. Indeed, FTY720 and phospho-FTY720 markedly upregulate CTGF and %%%collagen%%% type %%%IV%%% protein expressions. In addition, the tissue inhibitor of metalloproteinase-1 is transcriptionally activated by FTY720, whereas cytokine-induced matrix metalloproteinase-9 is down-regulated by FTY720. 4.--Depletion of the TGF-beta receptor type II by the siRNA transfection technique blocks not only Smad phosphorylation but also CTGF upregulation. Similarly, Smad-4 depletion by siRNA transfection also abrogates CTGF upregulation induced by FTY720 and phospho-FTY720. 5.--In summary, our data show that FTY720 and phospho-FTY720 not only activate the Smad signalling cascade in mesangial cells, but also upregulate the expression of CTGF and %%%collagen%%% . These findings suggest that FTY720 may have additional effects besides the established immunomodulatory action and, importantly, a profibrotic activity has to be considered in future experimental approaches.
Record Date Created: 20060124
Record Date Completed: 20070117

2/7/20 (Item 20 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

16251570 PMID: 15591053
Activation of STAT3%%%Smad1%%% is a key signaling pathway for progression to glomerulosclerosis in experimental glomerulonephritis.
Takahashi Toshikazu; Abe Hideharu; Arai Hidenori; Matsubara Takeshi; Nagai Kojiro; Matsuura Motokazu; Iehara Noriyuki; Yokode Masayuki; Nishikawa Shinichi; Kita Toru; Doi Toshio
Department of Clinical Biology and Medicine, Course of Biological Medicine, School of Medicine, The University of Tokushima, Tokushima, Japan.
Journal of biological chemistry (United States) Feb 25 2005, 280 (8) p7100-6, ISSN 0021-9258--Print Journal Code: 2985121R
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
Mesangial cell proliferation is a significant event in the development of progressive glomerular injuries. However, the issue of how cell proliferation is involved in the development of glomerulosclerosis is unclear. Recently, we showed that the overexpression of type %%%IV%%% %%%collagen%%% (Col %%%IV%%%), a major component of mesangial %%%extracellular%%% %%%matrix%%%, is transcriptionally regulated by %%%Smad1%%% in diabetic glomerulosclerosis. In this study, we have demonstrated the effect of the administration of an anti-platelet-derived growth factor (PDGF) beta-receptor antibody (APB5) blocking activation by the PDGF-B chain on rat glomerulonephritis and have examined the signaling pathways that regulate both glomerular cell proliferation and glomerulosclerosis in vivo and in vitro. Experimental mesangial proliferative glomerulonephritis (Thy1 GN) was induced by a single intravenous injection of anti-rat Thy-1.1 monoclonal antibody, in Thy1 GN, mesangial cell proliferation and the expression of Col %%%IV%%% peaked at day 6. Immunohistochemical staining for the expression of %%%Smad1%%%, phospho-%%%Smad1%%% (pSmad1), and phospho-STAT3 (pSTAT3) revealed that the peak for glomerular %%%Smad1%%% expression occurred at day 6, consistent with the peak for mesangial proliferation. The expression of pSmad1 was up-regulated at day 1, and the peak for glomerular pSmad1 expression occurred at day 4 of the disease. When treated with APB5, both mesangial proliferation and %%%sclerosis%%% were reduced significantly. The expression of %%%Smad1%%%, pSmad1, and pSTAT3 was also significantly reduced by the administration of APB5. PDGF induced both mesangial cell replication and Col %%%IV%%% synthesis in association with an increased expression of pSTAT3 and pSmad1 on cultured mesangial cells. In addition, APB5 reduced mesangial cell proliferation in association with decreased pSmad1, pSTAT3, and Col %%%IV%%% protein expressions in vitro. The introduction of dominant negative STAT3 significantly decreased the expression of Col %%%IV%%% in cultured mesangial cells. These data suggest that the activation of STAT3 and %%%Smad1%%% participates in the developing process of glomerulosclerosis in experimental glomerulonephritis.
Record Date Created: 20050221
Record Date Completed: 20050408
Date of Electronic Publication: 20041209

2/7/21 (Item 21 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

16104049 PMID: 15456771
Matrix GLA protein stimulates VEGF expression through increased transforming growth factor-beta1 activity in endothelial cells.
Bostrom Kristina; Zebboudj Amina F; Yao Yucheng; Lin Than S; Torres Alejandra
Division of Cardiology, David Geffen School of Medicine, University of California, Box 951679, Rm. 47-123 CHS, Los Angeles, CA 90095-1679, USA. kbostrom@mednet.ucla.edu

Journal of biological chemistry (United States) Dec 17 2004, 279 (51) p52904-13, ISSN 0021-9258--Print Journal Code: 2985121R
Contract/Grant No.: HL030568; HL; United States NHLBI; HL04270; HL; United States NHLBI
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
Matrix GLA protein (MGP) is expressed in endothelial cells (EC), and MGP deficiency results in developmental defects suggesting involvement in EC function. To determine the role of MGP in EC, we cultured bovine aortic EC with increasing concentrations of human MGP (hMGP) for 24 h. The results showed increased proliferation, migration, tube formation, and increased release of vascular endothelial growth factor-A (VEGF-A) and basic fibroblast growth factor (bFGF). HMGP, added endogenously or transiently expressed, increased VEGF gene expression dose-dependently as determined by real-time PCR. To determine the mechanism by which hMGP increased VEGF expression, we studied the effect of MGP on the activity of transforming growth factor (TGF)-beta1 compared with that of bone morphogenetic protein (BMP)-2 using transfection assays with TGF-beta- and BMP-response element reporter genes. Our results showed a strong enhancement of TGF-beta1 activity by hMGP, which was paralleled by increased VEGF expression. BMP-2 activity, on the other hand, was inhibited by hMGP. Neutralizing antibodies to TGF-beta blocked the effect of MGP on VEGF expression. The enhanced TGF-beta1 activity specifically activated the %%%Smad1%%% /5 pathway indicating that the TGF-beta receptor activin-like kinase 1 (ALK1) had been stimulated. It occurred without changes in expression of TGF-beta1 or ALK1 and was mimicked by transfection of constitutively active ALK1, which increased VEGF expression. Expression of VEGF and MGP was induced by TGF-beta1, but the induction of MGP preceded that of VEGF, consistent with a promoting effect on VEGF expression. Together, the results suggest that MGP plays a role in EC function, altering the response to TGF-beta superfamily growth factors.
Record Date Created: 20041213
Record Date Completed: 20050204
Date of Electronic Publication: 20040927

2/7/22 (Item 22 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

16026890 PMID: 15498344
[Bone morphogenetic protein-2-induced alpha 2 (I) collagen expression in odontoblastic MDPC-23 cells mediated by Smad proteins.]
He Wen-xi; Niu Zhong-ying; Zhao Shou-liang; Gao Jie; Li Ping
Department of Operative Dentistry, College of Stomatology, The Fourth Military Medical University, Xi'an 710032, China. hwenxi@yahoo.com.cn
Zhonghua kou qiang yi xue za zhi = Zhonghua kouqiang yixue zazhi = Chinese journal of stomatology (China) Sep 2004, 39 (5) p366-9, ISSN 1002-0098--Print Journal Code: 8711066
Publishing Model Print
Document type: English Abstract; Journal Article; Research Support, Non-U.S. Gov't
Languages: CHINESE
Main Citation Owner: NLM
Record type: MEDLINE, Completed
OBJECTIVE: To characterize the role of Smads proteins in alpha 2 (I) collagen (COL1A2) gene expression induced by bone morphogenetic protein-2 (BMP-2) in odontoblast cell line MDPC-23. METHODS: Endogenous Smad protein expression was determined by immunocytochemistry. Smads function and their role in COL1A2 gene expression were investigated in cotransfection experiments using promoter-luciferase reporter gene construct. RESULTS: MDPC-23 cells expressed %%%Smad1%%%, Smad5 and Smad6. BMP-2 promoted the activation of COL1A2 promoter reporter construct. Transient overexpression of %%%Smad1%%% or Smad5 was enhanced, while overexpression of Smad6 inhibited BMP-2-induced COL1A2 promoter activity. BMP-2 inducibility could be blocked by overexpression of %%%Smad1%%% or Smad5 dominant negative mutant. CONCLUSIONS: Smad signaling is functioning and appears to be involved in BMP-2-induced COL1A2 collagen transcription in MDPC-23. Smad signaling may play an important role in odontoblast differentiation and dentin %%%extracellular%%%, %%%matrix%%% formation mediated by BMP-2.
Record Date Created: 20041022
Record Date Completed: 20061109

2/7/23 (Item 23 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

15986060 PMID: 15452148
CD44 modulates %%%Smad1%%% activation in the BMP-7 signaling pathway.
Peterson Richard S; Andhare Roma A; Rousche Kathleen T; Knudson Warren; Wang Weihua; Grossfield Jami B; Thomas Raymond O; Hollingsworth Robert E; Knudson Cheryl B
Dept. of Biochemistry, Rush Medical College, Rush University Medical Center, 1653 West Congress Parkway, Chicago, IL 60612, USA.
Journal of cell biology (United States) Sep 27 2004, 166 (7) p1061-91, ISSN 0021-9525--Print Journal Code: 0375356
Contract/Grant No.: P50 AR 39239; AR; United States NIAMS; R01 AR 39507; AR; United States NIAMS; R01 AR 43384; AR; United States NIAMS
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed
Bone morphogenetic protein 7 (BMP-7) regulates cellular metabolism in embryonic and adult tissues. Signal transduction occurs through the activation of intracellular Smad proteins. In this paper, using a yeast two-hybrid screen, %%%Smad1%%% was found to interact with the cytoplasmic domain of CD44, a receptor for the %%%extracellular%%%, %%%matrix%%% macromolecule hyaluronan. Coimmunoprecipitation experiments confirmed the interaction of %%%Smad1%%% with full-length CD44-interactions that did not occur when CD44 receptors truncated within the cytoplasmic domain were tested. Chondrocytes overexpressing a truncated CD44 on a background of endogenous full-length CD44 no longer exhibited %%%Smad1%%% nuclear translocation upon BMP-7 stimulation. Further, pretreatment of chondrocytes with Streptomyces hyaluronidase to disrupt extracellular hyaluronan-cell interactions inhibited BMP-7-mediated %%%Smad1%%% phosphorylation, nuclear translocation of %%%Smad1%%% or Smad4, and SBE4-luciferase reporter activation. These results support a functional link between the BMP signaling cascade and CD44. Thus, changes in hyaluronan-cell interactions may serve as a means to modulate cellular responsiveness to BMP.
Record Date Created: 20040928
Record Date Completed: 20041202

2/7/24 (Item 24 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

15775398 PMID: 15148304
A hierarchical order of factors in the generation of FLK1- and SCL-expressing hematopoietic and endothelial progenitors from embryonic stem cells.
Park Changwon; Afrikanova Iva; Chung Yun Shin; Zhang Wen Jie; Arentson Elizabeth; Fong Gh Guo hua; Rosendahl Alexander; Choi Kyunghee
Department of Pathology and Immunology, 660 South Euclid Avenue, Campus Box 8118, St Louis, MO 63110, USA.
Development (Cambridge, England) (England) Jun 2004, 131 (11) p2749-62, ISSN 0950-1991--Print Journal Code: 8701744
Contract/Grant No.: R01 HL63736; HL; United States NHLBI
Publishing Model Print
Document type: Journal Article; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The receptor tyrosine kinase FLK1 and the transcription factor SCL play crucial roles in the establishment of hematopoietic and endothelial cell lineages in mice. We have previously used an in vitro differentiation model of embryonic stem (ES) cells and demonstrated that hematopoietic and endothelial cells develop via sequentially generated FLK1() and SCL() cells. To gain a better understanding of cellular and molecular events leading to hematopoietic specification, we examined factors necessary for FLK1() and SCL() cell induction in serum-free conditions. We demonstrate that bone morphogenetic protein (BMP) 4 was required for the generation of FLK1() and SCL() cells, and that vascular endothelial growth factor (VEGF) was necessary for the expansion and differentiation of SCL-expressing hematopoietic progenitors. Consistently, Flk1-deficient ES cells responded to BMP4 and generated TER119() and CD31() cells, but they failed to expand in response to VEGF. The %%%Smad1%%%/5 and map kinase pathways were activated by BMP4 and VEGF, respectively. The overexpression of SMAD6 in ES cells resulted in a reduction of FLK1() cells. In addition, a MAP kinase kinase 1 specific inhibitor blocked the expansion of SCL() cells in response to VEGF. Finally, VEGF mediated expansion of hematopoietic and endothelial cell progenitors was inhibited by TGFbeta1, but was augmented by activin A. Our studies suggest that hematopoietic and endothelial commitment from the mesoderm occurs via BMP4-mediated signals and that expansion and/or differentiation of such progenitors is achieved by an interplay of VEGF, TGFbeta1 and activin A signaling.
Record Date Created: 20040518
Record Date Completed: 20040728

2/7/25 (Item 25 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

15693177 PMID: 14732718
Type %%%IV%%% %%%collagen%%% is transcriptionally regulated by %%%Smad1%%% under advanced glycation end product (AGE) stimulation.
Abe Hideharu; Matsubara Takeshi; Iehara Noriyuki; Nagai Kojiro; Takahashi Toshikazu; Arai Hidenori; Kita Toru; Doi Toshio
Department of Clinical Biology and Medicine, University of Tokushima, Tokushima 770-8503, Japan.
Journal of biological chemistry (United States) Apr 2 2004, 279 (14) p14201-6, ISSN 0021-9258--Print Journal Code: 2985121R
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Prolonged exposure to hyperglycemia is now recognized as the most significant causal factor of diabetic complications. Excessive advanced glycation end products (AGEs) as a result of hyperglycemia in tissues or in the circulation may critically affect the progression of diabetic nephropathy. In diabetic nephropathy, glomerulosclerosis is a typical pathologic feature characterized by the increase of the %%%extracellular%%% %%%matrix%%% (ECM). We have reported previously that alpha1 type %%%IV%%% %%%collagen%%% (Col4) is one of the major components of ECM, which is up-regulated by AGEs, and that the overexpression of Col4 is transcriptionally regulated by an unknown transcription factor binding to the promoter. Here we identified this protein as %%%Smad1%%% by yeast one-hybrid screening. Using chromatin immunoprecipitation and reporter assay, we observed that %%%Smad1%%% directly regulated transcription for Col4 through the binding of %%%Smad1%%% to the promoter of Col4. %%%Smad1%%% was significantly induced along with Col4 in AGE-treated mesangial cells. Moreover, suppression of %%%Smad1%%% by antisense morpholino resulted in a decrease of AGE-induced Col4 overproduction. To elucidate the interaction between transforming growth factor-beta and %%%Smad1%%% , we investigated whether activin receptor-liked kinase1 (ALK1) was involved in this regulation. AGE stimulation significantly increased the expression of the ALK1 mRNA in mesangial cells. We also demonstrated that %%%Smad1%%% and ALK1 were highly expressed in human diabetic nephropathy. These results suggest that the modulation of %%%Smad1%%% expression is responsible for the initiation and progression of diabetic nephropathy and that blocking %%%Smad1%%% signaling may be beneficial in preventing diabetic nephropathy and other various diabetic complications.
Record Date Created: 20040329
Record Date Completed: 20040511
Date of Electronic Publication: 20040119

2/7/26 (Item 26 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

15660821 PMID: 15005012
Regulation of anabolic and catabolic gene expression in normal and osteoarthritic adult human articular chondrocytes by osteogenic protein-1.
Fan Z; Chubinskaya S; Rueger D C; Bau B; Haag J; Aigner T
Department of Pathology, University of Erlangen-Nurnberg, Krankenhausstr. 8-10, D-91054 Erlangen, Germany.
Clinical and experimental rheumatology (Italy) Jan-Feb 2004, 22 (1) p103-6, ISSN 0392-856X--Print Journal Code: 8308521
Contract/Grant No.: R01 47654; United States PHS
Publishing Model Print
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: Osteoarthritis is characterized by dramatic changes in chondrocyte metabolism including the overexpression of catabolic enzymes, but also a lack of anabolic activity. In this respect, osteogenic protein 1 (OP-1) appears to be one of the most potent anabolic factors of chondrocytes. In this study, we were interested in: (1) whether recombinant human OP-1 exerts its anabolic effects also on osteoarthritic chondrocytes, (2) whether OP-1 modulates the expression of catabolic genes, and (3) whether the BMP effects are related to the expression levels of its intracellular mediators (R- and I-Smads). METHODS: Chondrocytes were isolated from cartilage of either normal (n = 5) or osteoarthritic (n = 8) human knee joints and cultured in short-term high-density monolayer cultures with and without recombinant OP-1. RNA was isolated and analyzed for mRNA expression levels of anabolic (aggrecan, collagen type II), catabolic (MMP-1, -3, -13, ADAMTS-4), and intracellular signaling mediators (Smad 1, 4, 5, 6, 7, and 8) by quantitative online PCR. RESULTS: After OP-1 stimulation, the anabolic genes were significantly up-regulated in osteoarthritic chondrocytes in comparison to normal chondrocytes. Neither in normal nor osteoarthritic chondrocytes were significant changes observed for the matrix degrading enzymes. Smads were also expressed in both normal and osteoarthritic cells at roughly the same level with and without stimulation with OP-1. CONCLUSION: Osteoarthritic chondrocytes are not hypo-responsive to anabolic stimulation by OP-1. Thus, human recombinant OP-1 could be a suitable anabolic activator of osteoarthritic chondrocytes. This might be of particular interest as chondrocytes themselves showed very low levels of OP-1 expression.
Record Date Created: 20040309
Record Date Completed: 20040512

2/7/27 (Item 27 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

14493508 PMID: 11741887
Matrix GLA protein, a regulatory protein for bone morphogenetic protein-2.
Zebboudj Amina F; Imura Minori; Bostrom Kristina
Division of Cardiology, Department of Medicine, UCLA School of Medicine, Los Angeles, California 90095-1679, USA.
Journal of biological chemistry (United States) Feb 8 2002, 277 (6) p4388-94, ISSN 0021-9258--Print Journal Code: 2985121R
Contract/Grant No.: HL04270; HL; United States NHLBI
Publishing Model Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't; Research Support, U.S. Gov't, P.H.S.

Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE, Completed

Matrix GLA protein (MGP) has been identified as a calcification inhibitor in cartilage and vasculature. Part of this effect may be attributed to its influence on osteoinductive activity of bone morphogenetic protein-2 (BMP-2). To detect binding between MGP and BMP-2, we performed immunoprecipitation using MGP and BMP-2 tagged with FLAG and c-Myc. The results showed co-precipitation of BMP-2 with MGP. To quantify the effect of MGP on BMP-2 activity, we assayed for alkaline phosphatase activity and showed a dose-dependent effect. Low levels of MGP relative to BMP-2 (<1-fold excess) resulted in mild enhancement of osteoinduction, whereas intermediate levels (1-15-fold excess) resulted in strong inhibition. High levels of MGP (>15-fold excess), however, resulted in pronounced enhancement of the osteoinductive effect of BMP-2. Cross-linking studies showed that inhibitory levels of MGP abolished BMP-2 receptor binding. Immunoblotting showed a corresponding decrease in activation of %%%Smad1%%% , part of the BMP signaling system. Enhancing levels of MGP resulted in increased %%%Smad1%%% activation. To determine the cellular localization of BMP-2 in the presence of MGP, binding assays were performed on whole cells and cell-synthesized matrix. Inhibitory levels of MGP yielded increased matrix binding of BMP-2, suggesting that MGP inhibits BMP-2 in part via matrix association. These results suggest that MGP is a BMP-2 regulatory protein.

Record Date Created: 20020204
Record Date Completed: 20020305
Date of Electronic Publication: 20011206

2/7/28 (Item 28 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

14486248 PMID: 11811554

Stimulation of %%%Smad1%%% transcriptional activity by Ras-extracellular signal-regulated kinase pathway: a possible mechanism for collagen-dependent osteoblastic differentiation.

Suzawa Miyuki; Tamura Yasuhiro; Fukumoto Seiji; Miyazono Kohei; Fujita Toshiro; Kato Shigeaki; Takeuchi Yasuhiro

Institute of Molecular and Cellular Biosciences, University of Tokyo, Japan.

Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research (United States) Feb 2002, 17 (2) p240-8. ISSN 0884-0431--Print Journal Code: 8610640

Publishing Model Print

Document type: Journal Article; Research Support, Non-U.S. Gov't

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Signals from bone morphogenetic protein receptors (BMPRs) and cell adhesion to type I collagen are both important for osteoblastic differentiation and functions. BMP signals are mediated mostly by Smad and collagen signals are transduced by integrins to activate focal adhesion kinase (FAK) and its downstream molecules. This study was undertaken to clarify how %%%extracellular%%% %%%matrix%%% collagen signals converge with BMP actions. We show that integrin activation by collagen was involved in BMP signals because disruption of either collagen synthesis or collagen-alpha2beta1-integrin binding inhibited the stimulatory effect of BMP-2 on osteoblastic MC3T3-E1 cells. Downstream signals of collagen-integrin might be FAK-Ras-extracellular signal-regulated kinase (ERK) in osteoblastic cells. We further show that Ras-ERK signals enhanced the transcriptional activity of %%%Smad1%%% in response to BMP in these cells transiently transfected with expression plasmids for a constitutively active mutant RasV12, a dominant negative mutant RasN17, and an ERK phosphatase CL100. Ras-ERK signals did not augment the transcriptional activity of Smad3 in response to transforming growth factor beta (TGF-beta) receptor activation but that of %%%Smad1%%% in response to BMPR activation as examined in COS-1 cells. These observations suggest that the Ras-ERK pathway downstream of integrin-FAK is involved in %%%Smad1%%% signals activated by BMP and provide a possible mechanism for cooperation between intracellular signals activated by integrin and BMPRs in osteoblastic cells.

Record Date Created: 20020128
Record Date Completed: 20020802

2/7/29 (Item 29 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

12333900 PMID: 9261125

Transforming growth factor (TGF-beta)-specific signaling by chimeric TGF-beta type II receptor with intracellular domain of activin type IIB receptor.

Persson U; Souchelnytskyi S; Franzen P; Miyazono K, ten Dijke P, Heldin C H

Ludwig Institute for Cancer Research, Box 595, S-751 24 Uppsala, Sweden. Urban.Persson@LICR.uu.se

Journal of biological chemistry (UNITED STATES) Aug 22 1997, 272 (34) p21187-94. ISSN 0021-9258--Print Journal Code: 2985121R

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Members of the transforming growth factor-beta (TGF-beta) superfamily signal via different heteromeric complexes of two sequentially acting serine/threonine kinase receptors, i.e. type I and type II receptors. We generated two different chimeric TGF-beta superfamily receptors, i.e. TbetaR-I/BMPR-IB, containing the extracellular domain of TGF-beta type I receptor (TbetaR-I) and the intracellular domain of bone morphogenetic protein type IB receptor (BMPR-IB), and TbetaR-II/ActR-IIB, containing the extracellular domain of TGF-beta type II receptor (TbetaR-II) and the intracellular domain of activin type IIB receptor (ActR-IIB). In the presence of TGF-beta1, TbetaR-I/BMPR-IB and TbetaR-I/ActR-IIB formed heteromeric complexes with wild-type TbetaR-II and TbetaR-I, respectively, upon stable transfection in mink lung epithelial cell lines. We show that TbetaR-II/ActR-IIB restored the responsiveness upon transfection in mutant cell lines lacking functional TbetaR-II with respect to TGF-beta-mediated activation of a transcriptional signal, %%%extracellular%%% %%%matrix%%% formation, growth inhibition, and Smad phosphorylation. Moreover, TbetaR-I/BMPR-IB and TbetaR-II/ActR-IIB formed a functional complex in response to TGF-beta and induced phosphorylation of %%%Smad1%%%. However, complex formation is not enough for signal propagation, which is shown by the inability of TbetaR-I/BMPR-IB to restore responsiveness to TGF-beta in cell lines deficient in functional TbetaR-I. The fact that the TGF-beta1-induced complex between TbetaR-II/ActR-IIB and TbetaR-I stimulated endogenous Smad2 phosphorylation, a TGF-beta-like response, is in agreement with the current model for receptor activation in which the type I receptor determines signal specificity.

Record Date Created: 19970915
Record Date Completed: 19970915

2/7/30 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

0020176624 BIOSIS NO.: 200800225563

Spatial and temporal localization of components of the TGF-beta, BMP, 1HH and FGF signaling pathways in the postnatal mouse lumbar vertebral growth plate (LVGP)

AUTHOR: Dahia C (Reprint); Mahoney E; Durrani A; Wylie C

AUTHOR ADDRESS: Cincinnati Childrens Hosp, Med Ctr, Cincinnati, OH USA**USA

JOURNAL: Journal of Bone and Mineral Research 22 (Suppl. 1): pS157 SEP 2007 2007

CONFERENCE/MEETING: 29th Annual Meeting of the American-Society-for-Bone-and-Mineral-Research Honolulu, HI, USA September 16 -19, 2007; 20070916

SPONSOR: Amer Soc Bone & Mineral Res

ISSN: 0884-0431
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/31 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

0019846957 BIOSIS NO.: 200700506698
Induction of Smad1 by MT1-MMP contributes to tumor growth
AUTHOR: Freudenberg Jaclyn A; Chen Wen-Tien (Reprint)
AUTHOR ADDRESS: SUNY Stony Brook, Dept Med, HSC T15,Rm 053, Stony Brook, NY 11794 USA**USA
AUTHOR E-MAIL ADDRESS: wenchen@notes.cc.sunysb.edu
JOURNAL: International Journal of Cancer 121 (5): p966-977 SEP 1 2007 2007
ISSN: 0020-7136
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: MT1-MMP is a key integral membrane protease, which regulates tumor growth by cleaving %%%extracellular%%% %%%matrix%%% components, activating growth factors and receptors, and consequently, triggering downstream signals. To study what genes or pathways are mediated by endogenous MT1-MMP during tumor growth in vivo, we stably suppressed endogenous MT1-MMP in human tumor cells using RNA interference (RNAi). Tumor growth was significantly reduced in tumors derived from MT1-MMP-suppressed cells relative to control cells; the effect was rescued in cells engineered to re-express MT1-MMP expression. Gene expression profiling of cultured and tumor-derived cells by DNA microarray and realtime RT-PCR revealed that %%%Smad1%%% expression was upregulated in MT1-MMP-expressing cells and rapidly growing tumors; this was confirmed in 4 additional tumor cell lines. Furthermore, tumor growth of MT1-MMP-expressing cells was reduced when %%%Smad1%%% was suppressed by RNAi We also found that the active form, but not the latent form, of TGF-P was capable in promoting %%%Smad1%%% expression and 3D cell proliferation in MT1-MMP-suppressed cells. In addition, a dominant-negative form of the TGF-P Type 11 receptor reduced %%%Smad1%%% expression in MT1-MMP-expressing cells. Thus, we propose that MT1-MMP functions, in part, to promote tumor growth by inducing the expression of %%%Smad1%%% via TGF-beta signaling. (C) 2007 Wiley-Liss, Inc.

2/7/32 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

18817911 BIOSIS NO.: 200600163306
Type %%%IV%%% %%%collagen%%% is transcriptionally regulated by ALK1/%%%Smad1%%% signaling in diabetic nephropathy
AUTHOR: Abe Hideharu (Reprint); Matsubara Takeshi; Iehara Noriyuki; Nagai Kojiro; Takahashi Toshikazu; Arai Hidenori; Kita Toru; Doi Toshio
JOURNAL: Diabetes 53 (Suppl. 2): pA448 JUN 2004 2004
CONFERENCE/MEETING: 64th Annual Meeting of the American-Diabetes-Association Orlando, FL, USA June 04 -08, 2004; 20040604
SPONSOR: Amer Diabet Assoc
ISSN: 0012-1797
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/33 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

18672296 BIOSIS NO.: 200600017691
Expression of %%%smad1%%% is directly associated with glomerulosclerosis in diabetic nephropathy
AUTHOR: Matsubara Takeshi (Reprint); Abe Hideharu; Nagai Kojiro; Mima Akira ; Kanamori Hiroshi; Sumi Eriko; Takahashi Toshikazu, Matsuura Motokazu; Iehara Noriyuki; Fukatsu Atsushi; Kita Toru; Arai Hidenori; Doi Toshio
JOURNAL: Diabetes 54 (Suppl. 1): pA200 2005 2005
CONFERENCE/MEETING: 65th Annual Meeting of the American-Diabetes-Association San Diego, CA, USA June 10 -14, 2005; 20050610
SPONSOR: Amer Diabet Assoc
ISSN: 0012-1797
DOCUMENT TYPE: Meeting; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

2/7/34 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

18645085 BIOSIS NO.: 200510339585
Bone morphogenetic protein 7 is elevated in patients with chronic liver disease and exerts fibrogenic effects on human hepatic stellate cells
AUTHOR: Tacke Frank (Reprint); Gabele Erwin; Bataille Frauke; Schwabe Robert F; Froh Matthias; Wiest Reiner; Kleb! Frank; Straub Rainer H; Luedde Tom; Manns Michael P; Brenner David A; Schoelmerich Juergen; Schnabl Bernd
AUTHOR ADDRESS: Hannover Med Sch, D-3000 Hannover, Germany**Germany
JOURNAL: Hepatology 42 (4, Suppl. 1): p732A OCT 2005 2005
CONFERENCE/MEETING: 56th Annual Meeting of the American-Association-for-the-Study-of-Liver-Diseases San Francisco, CA, USA November 11 -15, 2005; 20051111
SPONSOR: Amer Assoc Study Liver Dis
ISSN: 0270-9139
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/35 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

17834166 BIOSIS NO.: 200400201799
Signal transduction pathway and smad activation by BMP - 9 in basal forebrain primary cells.
AUTHOR: Lopez-Coviella I (Reprint); Zemelko V; Berse B; Mellott T M; Blusztajn J K (Reprint)
AUTHOR ADDRESS: Psychiatry, Boston Univ. Med. Sch., Boston, MA, USA**USA
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2003 pAbstract No. 565.7 2003 2003
MEDIUM: e-file
CONFERENCE/MEETING: 33rd Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 08-12, 2003; 20031108
SPONSOR: Society of Neuroscience
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have previously shown that bone morphogenetic protein (BMP)-9, a member of the TGF-b superfamily of cytokines, is a differentiating factor for cholinergic central nervous system neurons. We have also reported that BMP-9 induced the expression of various genes encoding cell-cycle/growth control proteins, transcription factors, signal transduction molecules (receptor ligands, receptors, and modulators of signaling), %%%extracellular%%% %%%matrix%%% and adhesion molecules, enzymes, transporters, and chaperonins. However, whereas the basic mechanism of the TGF-b superfamily signal transduction pathway has been well characterized, little is known about the mediated signal transduction pathways of BMP-9. Here we describe the activation of Smad

proteins by BMP-9 in cells from basal forebrain of embryonic day (E)14 mice. Time-course experiments showed phosphorylation of %%%Smad1%%%, 5 and 8 that peaked 30 minutes following treatment with BMP-9, and subsided thereafter. No changes in inhibitory Smads (Smad 6 and Smad7) nor Smad4 (Co-Smad) were observed over time. When cells were treated with bFGF, there was an increase in the actual levels of %%%Smad1%%% and Smad5, an effect that may explain the potentiation of BMP-9 induced increase in acetylcholine levels by bFGF. Our data show that BMP-9 activates the same Smads and similar signal transduction pathway shared by other BMPs, which, in turn, may be responsible for the enhanced expression of genes that may mediate its actions as a cholinergic differentiating factor.

2/7/36 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

17716397 BIOSIS NO.: 200400085166
%%%Smad1%%% transcriptionally regulates type %%%IV%%% %%%collagen%%% expression, correlates with ALK1 in diabetic nephropathy.
AUTHOR: Abe Hideharu (Reprint); Matsubara Takeshi; Iehara Noriyuki; Nagai Kojiro; Takahashi Toshikazu (Reprint); Arai Hidenori, Kita Toru; Doi Toshio (Reprint)
AUTHOR ADDRESS: Department of Clinical Biology and Medicine, University of Tokushima, Tokushima, Japan**Japan
JOURNAL: Journal of the American Society of Nephrology 14 (Abstracts Issue): p5A November 2003 2003
MEDIUM: print
CONFERENCE/MEETING: Meeting of the American Society of Nephrology Renal Week San Diego, CA, USA November 12-17, 2003; 20031112
SPONSOR: American Society of Nephrology
ISSN: 1046-6673
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

2/7/37 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

17653168 BIOSIS NO.: 200400023925
ELF IS A KEY ADAPTOR FOR TGF-beta SIGNALING, LIVER DEVELOPMENT AND HEPATOCELLULAR CANCER.
AUTHOR: Tang Yi (Reprint); Katuri Varalakshmi (Reprint); Dillner Allan (Reprint); Danovitch Stuart (Reprint); Mishra Bibhuti (Reprint); Mishra Lopa (Reprint)
AUTHOR ADDRESS: Washington, DC, USA**USA
JOURNAL: Digestive Disease Week Abstracts and Itinerary Planner 2003 p Abstract No. 267 2003 2003
MEDIUM: e-file
CONFERENCE/MEETING: Digestive Disease 2003 FL, Orlando, USA May 17-22, 2003; 20030517
SPONSOR: American Association for the Study of Liver Diseases
American Gastroenterological Association
American Society for Gastrointestinal Endoscopy
Society for Surgery of the Alimentary Tract
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT. Background. TGF-beta modulates angiogenesis, organogenesis, and promotes carcinogenesis. Signaling is mediated by Smad proteins and cytoplasmic adaptors. We have shown that disruption of the adaptor protein ELF, disrupts TGF-b signaling in mice (Science 2002, in press). The elf -/- mutant phenotype, is similar to that seen in smad2/smad3 mutants with defective liver formation. ELF deficient mice show a yolk sac angiogenesis phenotype similar to that of Smad5. Endothelial cells surrounding newly specified hepatic tissue, promote morphogenesis and organ development. Also ELF interacts with Smad4 a gastrointestinal tumor suppressor. Aims: To test: 1. disrupted angiogenesis and liver formation in elf -/- mutants, 2. ELF association with %%%Smad1%%% or Smad5, 3. If loss of ELF results in hepatocellular carcinogenesis. Methods and Results: 1. Immunoblot and Immunohistochemical labeling of wild type and elf mutant embryonic tissue showed reduced expression of flk-1 and pecam in elf -/- embryonic liver. Reduced expression of alpha -fetoprotein and cytokeratin in elf -/- embryonic liver along with abnormal hepatocytes and bile ducts indicated arrested differentiation and growth, resulting in liver hypoplasia. 2. %%%Smad1%%% and Smad5 expression were similar in the elf -/- mutants to controls. There was no association between ELF and %%%Smad1%%% or Smad5. 3. Follow up of 18 elf mutant mice for 12 months revealed multiple foci of hepatocyte dysplasia with 2 hepatocellular carcinomas and 1 renal cell carcinoma with none in the controls. Albumin and alpha -fetoprotein expression increased in liver tissues of elf adult mice, especially with tumors. Conclusions: 1. These studies support a role for ELF in liver organogenesis. 2. ELF involvement in angiogenesis occurs through the ALK5-Smad3/4. In TGF-b the yolk sac phenotype can be divided into two groups: a) TGF-b1 bound to endoglin-TGF-b Receptor II or TbRII-ALK-5 yolk sac vessel formation for endothelial cell proliferation, differentiation and %%%extracellular%%% %%%matrix%%% formation are affected, b) TGF-b1 bound to endoglin-TbRII- ALK-1, Smad5 phosphorylation, yolk sac vasculature, and vascular smooth muscle cells with mesenchymal cell differentiation and a mature vascular tree are affected. As %%%Smad1%%% and Smad5 do not interact with ELF and are expressed equally in wt and elf mutant tissues, we speculate that ELF is involved in the TGF-b1-endoglin-TGF-b Receptor II or TbRII-ALK-5 pathway. 3. These results indicate that ELF Spectrins may behave as a tumor suppressor through TGF-beta signaling in mice..

2/7/38 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

16727669 BIOSIS NO.: 200200321180
Mechanical stretch down-regulates negative feedback action of TGF-beta superfamily through augmentation of phosphorylated SMADs in rat mesangial cells (MC)
AUTHOR: Hayashi Yoshimitsu (Reprint); Asano Kenichiro (Reprint); Sanada Hironobu (Reprint); Katoh Tetsuo (Reprint); Watanabe Tsuyoshi (Reprint)
AUTHOR ADDRESS: Internal Medicine III, Fukushima Medical University, Fukushima, Japan**Japan
JOURNAL: Journal of the American Society of Nephrology 12 (Program and Abstract Issue): p815A September, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: ASN (American Society of Nephrology)/ISN (International Society of Nephrology) World Congress of Nephrology San Francisco, CA, USA October 10-17, 2001; 20011010
ISSN: 1046-6673
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

2/7/39 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2008 The Thomson Corporation. All rts. reserv.

16557245 BIOSIS NO.: 200200150756
Transforming growth factor-beta repression of matrix metalloproteinase-1 in dermal fibroblasts involves Smad3
AUTHOR: Yuan Weihua; Varga John (Reprint)
AUTHOR ADDRESS: Section of Rheumatology, University of Illinois at Chicago College of Medicine, 900 S. Ashland Ave., Rm. 1158 MBRB, Chicago, IL, 60607-7171, USA**USA
JOURNAL: Journal of Biological Chemistry 276 (42): p38502-38510 October 19, 2001 2001
MEDIUM: print
ISSN: 0021-9258

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Enhanced production of matrix metalloproteinase-1 (MMP-1, collagenase-1) is implicated in pathological tissue destruction. Transforming growth factor-beta (TGF-beta) prevents cytokine-induced MMP-1 gene expression in fibroblasts. In these studies, we examined the hypothesis that repression of MMP-1 may be mediated through the Smad signaling pathway. The results showed that Smad3 and Smad4, but not %%%Smad1%%%, or Smad2, mimicked the inhibitory effect of TGF-beta and abrogated interleukin-1 beta (IL-1beta)-induced stimulation of MMP-1 promoter activity and NFkappaB-specific gene transcription in dermal fibroblasts. Experiments with truncation mutants indicated that both MH1 and MH2 domains of Smad3 were necessary for inhibitory activity. Dominant negative mutants of Smad3 or Smad4 and antagonistic Smad7, which disrupts ligand-induced Smad3 phosphorylation, abrogated the repression of MMP-1 transcription by TGF-beta. Similar results were obtained using immunoblot and Northern analysis. Furthermore, TGF-beta failed to repress MMP-1 promoter activity in Smad3-deficient murine embryonic fibroblasts. These results implicated cellular Smads in mediating the inhibitory effects of TGF-beta. Overexpression of the transcriptional co-activator p300, but not its histone acetyltransferase (HAT)-deficient mutant, was able to relieve repression of MMP-1 gene expression, suggesting that Smad-dependent inhibition may be due to increased competition between Smad proteins and IL-1-beta signaling pathways for limiting amounts of cellular p300. Together, these results demonstrate that MMP-1 is a target for negative regulation by TGF-beta through cellular Smad3 and Smad4. Smad-mediated repression of MMP-1 gene expression may be important for preventing excessive matrix degradation induced by inflammatory cytokines; disruption of Smad signaling, as occurs in certain cancer cells, may thus be causally linked to uncontrolled tissue destruction mediated through MMP-1.

2/7/40 (Item 1 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE
(c) 2008 Elsevier B.V. All rts. reserv.

04212104 2008277718
Amelogenin binds to both heparan sulfate and bone morphogenetic protein 2 and pharmacologically suppresses the effect of noggin
Saito K.; Konishi I.; Nishiguchi M.; Hoshino T.; Fujiwara T.
ADDRESS: T. Hoshino, Division of Pediatric Dentistry, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8588, Japan
EMAIL: thoshino@nagasaki-u.ac.jp
Journal: Bone, 43/2 (371-376), 2008, United States
CODEN: BONED
ISSN: 8756-3282
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 41

Enamel matrix derivative (EMD) is widely considered useful to promote tissue regeneration during periodontal treatment. It has been reported that the main constituent of EMD is amelogenin and that the BMP-like and TGF-beta-like activity of EMD promotes osteogenesis. However, it remains unclear whether those activities are dependent on amelogenin or another growth factor contained in EMD. We performed two-dimensional SDS-PAGE analysis of EMD, as well as Western blot analyses using anti-amelogenin, anti-BMP2/4, and anti-TGF-beta1 antibodies, and amino acid sequencing. Our results revealed that a large number of splicing forms of amelogenin, BMP2/4, and other unknown molecules were involved in EMD, though TGF-beta1 was not. In addition, we have evaluated intracellular signaling of ERK1/2 and %%%Smad1%%%/5/8, binding potential and alkaline phosphatase activity and have explored the potential regulatory relationship between amelogenin and BMP. Amelogenin bound to BMP2 as well as heparin/heparan sulfate. Thus, it was suggested that BMP2/4 carried over in EMD during processing promote binding activity and phosphorylate %%%Smad1%%%/5/8 in osteoblasts. On the other hand, amelogenin did not phosphorylate %%%Smad1%%%/5/8, but rather ERK1/2. Further, high-density amelogenin reduced the inhibition of alkaline phosphatase activity by noggin, though amelogenin did not have antagonistic properties against BMP. Together with the above findings, our findings suggest that the BMP2/4 contaminated during the purification process of EMD because of the avidity of amelogenin plays an important role in signaling pathway of calcification. (c) 2008 Elsevier Inc. All rights reserved.

2/7/41 (Item 2 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE
(c) 2008 Elsevier B.V. All rts. reserv.

04135006 2008171151
Asymmetric mitosis: Unequal segregation of proteins destined for degradation
Fuentealba L.C.; Eivers E.; Geissert D.; Taelman V.; De Robertis E.M.
ADDRESS: E. M. De Robertis, Howard Hughes Medical Institute, Department of Biological Chemistry, University of California, Los Angeles, CA 90095-1662, United States
EMAIL: edderobertis@mednet.ucla.edu
Journal: Proceedings of the National Academy of Sciences of the United States of America, 105/22 (7732-7737), 2008, United States
PUBLICATION DATE: June 3, 2008
CODEN: PNASA
ISSN: 0027-8424 eISSN: 1091-6490
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 32

Mitotic cell division ensures that two daughter somatic cells inherit identical genetic material. Previous work has shown that signaling by the %%%Smad1%%% transcription factor is terminated by polyubiquitinylation and proteasomal degradation after essential phosphorylations by MAPK and glycogen synthase kinase 3 (GSK3). Here, we show that, unexpectedly, proteins specifically targeted for proteasomal degradation are inherited preferentially by one mitotic daughter during somatic cell division. Experiments with dividing human embryonic stem cells and other mammalian cultured cell lines demonstrated that in many supposedly equal mitoses the segregation of proteins destined for degradation (%%%Smad1%%% phosphorylated by MAPK and GSK3, phospho-beta-catenin, and total polyubiquitinylated proteins) was asymmetric. Transport of pSmad1 targeted for degradation to the centrosome required functional microtubules. In vivo, an antibody specific for Mad phosphorylated by MAPK showed that this antigen was associated preferentially with one of the two centrosomes in Drosophila embryos at cellular blastoderm stage. We propose that this remarkable cellular property may be explained by the asymmetric inheritance of peripheral centrosomal proteins when centrioles separate and migrate to opposite poles of the cell, so that one mitotic daughter remains pristine. We conclude that many mitotic divisions are unequal, unlike what was previously thought. (c) 2008 by The National Academy of Sciences of the USA.

2/7/42 (Item 3 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE
(c) 2008 Elsevier B.V. All rts. reserv.

03717641 2007096464
Antisense targeting of TGF-beta1 augments BMP-induced upregulation of osteopontin, type I collagen and Cbfa1 in human Saos-2 cells
Shen Z.-J.; Kook Kim S.; Youn Jun D.; Park W.; Ho Kim Y.; Malter J.S.; Jo Moon B.
ADDRESS: Z.-J. Shen, Department of Biochemistry, College of Natural Sciences, Kyungpook National University, Taegu, 702-701, South Korea
EMAIL: zshen2@wisc.edu
Journal: Experimental Cell Research, 313/7 (1415-1425), 2007, United States
PUBLICATION DATE: April 15, 2007
CODEN: ECREA

ISSN: 0014-4827
PUBLISHER ITEM IDENTIFIER: S0014482707000377
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 60

Despite commonalities in signal transduction in osteoblasts from different species, the role of TGF-beta1 on bone formation remains elusive. In particular, the role of autocrine TGF-beta1 on human osteoblasts is largely unknown. Here we show the effect of TGF-beta1 knock-down on the proliferation and differentiation of osteoblasts induced by BMP2. Treatment with antisense TGF-beta1 moderately increased the rate of cell proliferation, which was completely reversed by the exogenous addition of TGF-beta1. Notably, TGF-beta1 blockade significantly enhanced BMP2-induced upregulation of mRNAs encoding osteopontin, type I collagen and Cbfa1, which was suppressed by exogenous TGF-beta1. Moreover, TGF-beta1 knock-down increased BMP2-induced phosphorylation of %%%Smad1%%%/5 as well as their nuclear import, which paralleled a reduction of inhibitory Smad6. These data suggest autocrine TGF-beta1 antagonizes BMP signaling through modulation of inducible Smad6 and the activity of BMP specific %%%Smad1%%% /5. (c) 2007 Elsevier Inc. All rights reserved.

2/7/43 (Item 4 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE
(c) 2008 Elsevier B.V. All rts. reserv.

03582744 2007002946
Differential regulation of steroidogenesis by bone morphogenetic proteins in granulosa cells: Involvement of extracellularly regulated kinase signaling and oocyte actions in follicle-stimulating hormone-induced estrogen production
Miyoshi T.; Otsuka F.; Inagaki K.; Otani H.; Takeda M.; Suzuki J.; Goto J.; Ogura T.; Makino H.
ADDRESS: Dr. F. Otsuka, Department of Medicine and Clinical Science, Okayama University, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama City, 700-8558 , Japan
EMAIL: fumiotsu@md.okayama-u.ac.jp
Journal: Endocrinology, 148/1 (337-345), 2007, United States
CODEN: ENDOA
ISSN: 0013-7227 eISSN: 0013-7227
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 37

In the present study, we investigated the cellular mechanism by which oocytes and bone morphogenetic proteins (BMPs) govern FSH-induced steroidogenesis using rat primary granulosa cells. BMP-6 and BMP-7 both inhibited FSH- and forskolin (FSK)-induced progesterone synthesis and reduced cAMP synthesis independent of the presence or absence of oocytes. BMP-7 also increased FSH-induced estradiol production, and the response was further augmented in the presence of oocytes. In contrast, BMP-6 had no impact on estradiol synthesis regardless of the presence of oocytes. Because BMP-7 changed neither FSK- nor cAMP-induced estradiol production, the BMP-7 action was mediated through a FSH receptor signaling mechanism that was independent of cAMP-protein kinase A pathway. Treatment with FSH but not cAMP activated ERK1/2 phosphorylation in granulosa cells, which was further accelerated by oocytes. A specific ERK inhibitor, U0126, increased estradiol production and decreased FSH- and FSK-induced progesterone production and cAMP synthesis. This suggests that ERK activation is directly linked to inhibition of estradiol synthesis and amplification of cAMP. Moreover, FSH-induced ERK1/2 phosphorylation was inhibited by BMP-7 but not influenced by BMP-6. In contrast, BMP signaling including %%%Smad1%%%/5/8 phosphorylation and Id-1 transcription was up-regulated by FSH and oocytes in granulosa cells through inhibition of Smad6/7 expression. Collectively, oocytes enhance FSH-induced MAPK activation and BMP signaling in granulosa cells, which leads to differential regulation of steroidogenesis elicited by BMPs in the presence of FSH in developing follicles. Copyright (c) 2007 by The Endocrine Society.

2/7/44 (Item 5 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE
(c) 2008 Elsevier B.V. All rts. reserv.

03199922 2006012652
Embryonic dorsal-ventral signaling: Secreted Frizzled-related proteins as inhibitors of tolloid proteinases
Lee H.X.; Ambrosio A.L.; Reversade B.; De Robertis E.M.
ADDRESS: E.M. De Robertis, Howard Hughes Medical Institute, Department of Biological Chemistry, University of California, Los Angeles, CA 90095, United States
EMAIL: ederobertis@mednet.ucla.edu
Journal: Cell, 124/1 (147-159), 2006, United States
PUBLICATION DATE: January 13, 2006
CODEN: CELLB
ISSN: 0092-8674
PUBLISHER ITEM IDENTIFIER: S0092867405014133
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 42

Here we report an unexpected role for the secreted Frizzled-related protein (sFRP) Sizzled/Ogon as an inhibitor of the extracellular proteolytic reaction that controls BMP signaling during Xenopus gastrulation. Microinjection experiments suggest that the Frizzled domain of Sizzled regulates the activity of Xolloid-related (Xlr), a metalloproteinase that degrades Chordin, through the following molecular pathway: Szl (reverse turnstile) Xlr (reverse turnstile) Chd (reverse turnstile) BMP --> P-%%%Smad1%%% --> Szl. In biochemical assays, the Xlr proteinase has similar affinities for its endogenous substrate Chordin and for its competitive inhibitor Sizzled, which is resistant to enzyme digestion. Extracellular levels of Sizzled and Chordin in the gastrula embryo and enzyme reaction constants were all in the 10SUP-8 M range, consistent with a physiological role in the regulation of dorsal-ventral patterning. Sizzled is also a natural inhibitor of BMP1, a Tolloid metalloproteinase of medical interest. Furthermore, mouse sFRP2 inhibited Xlr, suggesting a wider role for this molecular mechanism. (c)2006 Elsevier Inc.

2/7/45 (Item 6 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE
(c) 2008 Elsevier B.V. All rts. reserv.

02960802 2005117864
Twisted gastrulation and chordin inhibit differentiation and mineralization in MC3T3-E1 osteoblast-like cells
Petryk A.; Shimmi O.; Jia X.; Carlson A.E.; Tervonen L.; Jarcho M.P.; O'Connor M.B.; Gopalakrishnan R.
ADDRESS: R. Gopalakrishnan, Department of Oral Sciences, Univ. of MN School of Dentistry, 16-108S Moos Tower, 515 Delaware Street SE, Minneapolis, MN 55455, United States
EMAIL: gopal007@umn.edu
Journal: Bone, 36/4 (617-626), 2005, United States
CODEN: BONED
ISSN: 8756-3282
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 60

Bone morphogenetic proteins (BMPs) are potent inducers of osteoblast differentiation. The accessibility of BMP ligands for binding to their receptors is regulated by secreted proteins Twisted gastrulation (Tsg) and Chordin (Chd). Tsg antagonizes BMP signaling by forming ternary complexes with Chd and BMPs, thereby preventing BMPs from binding to their receptors. In addition to the anti-BMP function, Tsg also has pro-BMP activity, partly mediated by cleavage and degradation of Chd, which releases BMPs from ternary complexes. The roles of Tsg and Chd in osteoblast differentiation are not known. Therefore, in the present study, we investigated the effect

of exogenous Tsg and Chd on osteoblast differentiation and mineralization using a well-characterized subclone of MC3T3-E1 osteoblast-like cells. Our results show that Tsg and Chd are expressed in MC3T3-E1 osteoblast-like cells. While Tsg mRNA levels decrease during osteoblast differentiation, Chd levels are found to increase. Tsg and Chd proteins accumulate in the cell culture media as the osteoblasts differentiate. Exogenous Tsg and Chd inhibit osteoblast differentiation and mineralization. Osteocalcin (OCN) mRNA levels decrease following both Tsg and Chd treatment. Tsg and Chd also inhibit alkaline phosphatase (ALP) activity in a dose-dependent manner. To provide insight into the mechanism of Tsg and Chd action, we investigated the effect of Tsg and Chd on BMP activity by determining phosphorylated %%%Smad1%%% (pSmad1) levels. We show that both Tsg and Chd can independently and in combination reduce pSmad1 levels in MC3T3-E1 cells treated with BMP4. Further, BMP2 partially reverses the inhibitory effect of Tsg and Chd on ALP activity. Taken together, these results suggest that Tsg and Chd are involved in osteoblast differentiation and mineralization by regulating BMP signaling. (c) 2005 Elsevier Inc. All rights reserved.

2/7/46 (Item 7 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE
(c) 2008 Elsevier B.V. All rts. reserv.

00883201 1998126515
Direct binding of Smad3 and Smad4 to critical TGFbeta-inducible elements in the promoter of human plasminogen activator inhibitor-type 1 gene
Dennler S.; Itoh S.; Vivien D.; Ten Dijke P.; Huet S.; Gauthier J.-M.
ADDRESS: J.-M. Gauthier, Labaratoire GlaxoWellcome, 25 avenue du Quebec, 91951 Les Ulis Cedex, France
EMAIL: jmg49499@GlaxoWellcome.co.uk
Journal: EMBO Journal, 17/11 (3091-3100), 1998, United Kingdom
PUBLICATION DATE: June 1, 1998
CODEN: EMJOD
ISSN: 0261-4189
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 59

Smad proteins play a key role in the intracellular signalling of transforming growth factor beta (TGFbeta), which elicits a large variety of cellular responses. Upon TGFbeta receptor activation, Smad2 and Smad3 become phosphorylated and form heteromeric complexes with Smad4. These complexes translocate to the nucleus where they control expression of target genes. However, the mechanism by which Smads mediate transcriptional regulation is largely unknown. Human plasminogen activator inhibitor-1 (PAI-1) is a gene that is potently induced by TGFbeta. Here we report the identification of Smad3/Smad4 binding sequences, termed CAGA boxes, within the promoter of the human PAI-1 gene. The CAGA boxes confer TGFbeta and activin, but not bone morphogenetic protein (BMP) stimulation to a heterologous promoter reporter construct. Importantly, mutation of the three CAGA boxes present in the PAI-1 promoter was found to abolish TGFbeta responsiveness. Thus, CAGA elements are essential and sufficient for the induction by TGFbeta. In addition, TGFbeta induces the binding of a Smad3/Smad4-containing nuclear complex to CAGA boxes. Furthermore, bacterially expressed Smad3 and Smad4 proteins, but not %%%Smad1%%% nor Smad2 protein, bind directly to this sequence in vitro. The presence of this box in TGFbeta-responsive regions of several other genes suggests that this may be a widely used motif in TGFbeta-regulated transcription.

2/7/47 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE
(c) 2008 Elsevier B.V. All rts. reserv.

0082586348 EMBASE No: 2008376239
BMP signaling dynamics in embryonic orofacial tissue
Mukhopadhyay P.; Webb C.L.; Warner D.R.; Greene R.M.; Pisano M.M.
Department of Molecular, Cellular and Craniofacial Biology, University of Louisville Birth Defects Center, University of Louisville, Louisville, KY 40292, United States, Birth Defects Center, ULSD, University of Louisville, 501 S. Preston Street, Louisville, KY 40292, United States
AUTHOR EMAIL: p0mukh01@louisville.edu
CORRESP. AUTHOR/AFFIL: Mukhopadhyay P.: Birth Defects Center, ULSD, University of Louisville, 501 S. Preston Street, Louisville, KY 40292, United States
CORRESP. AUTHOR EMAIL: p0mukh01@louisville.edu

Journal of Cellular Physiology (J. Cell. Physiol.) (United States) September 1, 2006, 216/3 (771-779)
CODEN: JCLLA ISSN: 0021-9541
DOI: 10.1002/jcp.21455
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 65

The bone morphogenetic protein (BMP) family represents a class of signaling molecules, that plays key roles in morphogenesis, cell proliferation, survival and differentiation during normal development. Members of this family are essential for the development of the mammalian orofacial region where they regulate cell proliferation, %%%extracellular%%% %%%matrix%%% synthesis, and cellular differentiation. Perturbation of any of these processes results in orofacial clefting. Embryonic orofacial tissue expresses BMP mRNAs, their cognate proteins, and BMP-specific receptors in unique temporo-spatial patterns, suggesting functional roles in orofacial development. However, specific genes that function as downstream mediators of BMP action during orofacial ontogenesis have not been well defined. In the current study, elements of the Smad component of the BMP intracellular signaling system were identified and characterized in embryonic orofacial tissue and functional activation of the Smad pathway by BMP2 and BMP4 was demonstrated. BMP2 and BMP4-initiated Smad signaling in cells derived from embryonic orofacial tissue was found to result in: (1) phosphorylation of Smads 1 and 5; (2) nuclear translocation of Smads 1, 4, and 5; (3) binding of Smads 1, 4, and 5 to a consensus Smad binding element (SBE)-containing oligonucleotide; (4) transactivation of transfected reporter constructs, containing BMP-inducible Smad response elements; and (5) increased expression at transcriptional as well as translational levels of Id3 (endogenous gene containing BMP receptor-specific Smad response elements). Collectively, these data document the existence of a functional Smad-mediated BMP signaling system in cells of the developing murine orofacial region. (c) 2008 Wiley-Liss, Inc.

2/7/48 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE
(c) 2008 Elsevier B.V. All rts. reserv.

0082311061 EMBASE No: 2008112363
Fibrosis in Systemic %%%Sclerosis%%%
Varga J.A.; Trojanowska M.
Division of Rheumatology, Northwestern University Feinberg School of Medicine, McGaw 2300, 240 East Huron Street, Chicago, IL 60611-2909, United States
AUTHOR EMAIL: j-varga@northwestern.edu
CORRESP. AUTHOR/AFFIL: Varga J.A.: Division of Rheumatology, Northwestern University Feinberg School of Medicine, McGaw 2300, 240 East Huron Street, Chicago, IL 60611-2909, United States
CORRESP. AUTHOR EMAIL: j-varga@northwestern.edu

Rheumatic Disease Clinics of North America (Rheum. Dis. Clin. North Am.) (United States) February 1, 2008, 34/1 (115-143)
CODEN: RDCAE ISSN: 0889-857X
PUBLISHER ITEM IDENTIFIER: S0889857X07000944
DOI: 10.1016/j.rdc.2007.11.002
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 132

This article reviews current understanding of the pathophysiology of fibrosis in systemic %%%sclerosis%%%. It highlights recent discoveries, insights, and emerging research, and potential opportunities for the development of targeted antifibrotic therapies. (c) 2008 Elsevier Inc. All

rights reserved.

2/7/49 (Item 3 from file: 72)
DIALOG(R)File 72:EMBASE
(c) 2008 Elsevier B.V. All rts. reserv.

0082292855 EMBASE No: 2008090617
A human bone morphogenetic protein antagonist is down-regulated in renal cancer
Blish K.R., Wang W., Willingham M.C., Du W., Birse C.E., Krishnan S.R., Brown J.C., Hawkins G.A., Garvin A.J., D'Agostino Jr. R.B., Torti F.M., Torti S.V.
Section on Molecular Medicine, Section on Biostatistics, Wake Forest University School of Medicine, Winston-Salem, NC 27157-0001, United States
AUTHOR EMAIL: storti@wfubmc.edu
CORRESP. AUTHOR/AFFIL: Torti S.V.: Department of Biochemistry, Section on Biostatistics, Wake Forest University School of Medicine, Winston-Salem, NC 27157-0001, United States
CORRESP. AUTHOR EMAIL: storti@wfubmc.edu

Molecular Biology of the Cell (Mol. Biol. Cell) (United States)
February 1, 2008, 19/2 (457-464)
CODEN: MBCEE ISSN: 1059-1524
DOI: 10.1091/mbc.E07-05-0433
URL: http://www.molbiolcell.org/cgi/reprint/19/2/457
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 45

We analyzed expression of candidate genes encoding cell surface or secreted proteins in normal kidney and kidney cancer. This screen identified a bone morphogenetic protein (BMP) antagonist, SOSTDC1 (sclerostin domain-containing-1) as down-regulated in kidney tumors. To confirm screening results, we probed cDNA dot blots with SOSTDC1. The SOSTDC1 message was decreased in 20/20 kidney tumors compared with normal kidney tissue. Immunohistochemistry confirmed significant decrease of SOSTDC1 protein in clear cell renal carcinomas relative to normal proximal renal tubule cells ($p < 0.001$). Expression of SOSTDC1 was not decreased in papillary and chromophobe kidney tumors. SOSTDC1 was abundantly expressed in podocytes, distal tubules, and transitional epithelia of the normal kidney. Transfection experiments demonstrated that SOSTDC1 is secreted and binds to neighboring cells and/or the %%%extracellular%%% %%%matrix%%%. SOSTDC1 suppresses both BMP-7-induced phosphorylation of R-Smads-1, -5, and -8 and Wnt-3a signaling. Restoration of SOSTDC1 in renal clear carcinoma cells profoundly suppresses proliferation. Collectively, these results demonstrate that SOSTDC1 is expressed in the human kidney and decreased in renal clear cell carcinoma. Because SOSTDC1 suppresses proliferation of renal carcinoma cells, restoration of SOSTDC1 signaling may represent a novel target in treatment of renal clear cell carcinoma. (c) 2008 by The American Society for Cell Biology.

2/7/50 (Item 4 from file: 72)
DIALOG(R)File 72:EMBASE
(c) 2008 Elsevier B.V. All rts. reserv.

0082104555 EMBASE No: 2008131754
Role of transforming growth factor-beta superfamily signaling pathways in human disease
Gordon K.J., Blobe G.C.
Department of Pharmacology and Cancer Biology, Duke University, Durham, NC, United States
AUTHOR EMAIL: blobe001@mc.duke.edu
CORRESP. AUTHOR/AFFIL: Blobe G.C.: Department of Pharmacology and Cancer Biology, Duke University, Durham, NC, United States
CORRESP. AUTHOR EMAIL: blobe001@mc.duke.edu

Biochimica et Biophysica Acta - Molecular Basis of Disease (Biochim. Biophys. Acta Mol. Basis Dis.) (Netherlands) April 1, 2008, 1782/4 (197-228)
CODEN: BBADE ISSN: 0925-4439
PUBLISHER ITEM IDENTIFIER: S092544390800029X
DOI: 10.1016/j.bbadis.2008.01.006
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 393

Transforming growth factor beta (TGF-beta) superfamily signaling pathways are ubiquitous and essential regulators of cellular processes including proliferation, differentiation, migration, and survival, as well as physiological processes, including embryonic development, angiogenesis, and wound healing. Alterations in these pathways, including either germ-line or somatic mutations or alterations in the expression of members of these signaling pathways often result in human disease. Appropriate regulation of these pathways is required at all levels, particularly at the ligand level, with either a deficiency or an excess of specific TGF-beta superfamily ligands resulting in human disease. TGF-beta superfamily ligands and members of these TGF-beta superfamily signaling pathways also have emerging roles as diagnostic, prognostic or predictive markers for human disease. Ongoing studies will enable targeting of TGF-beta superfamily signaling pathways for the chemoprevention and treatment of human disease. (c) 2008 Elsevier B.V. All rights reserved.

2/7/51 (Item 5 from file: 72)
DIALOG(R)File 72:EMBASE
(c) 2008 Elsevier B.V. All rts. reserv.

0081729372 EMBASE No: 2007163217
TGF-beta signaling in vascular fibrosis
Ruiz-Ortega M.; Rodriguez-Vita J.; Sanchez-Lopez E.; Carvajal G.; Egido J.
Vascular and Renal Research Laboratory, Fundacion Jimenez Diaz, Universidad Autonoma Madrid, Avda. Reyes Catolicos, 2, 28040 Madrid, Spain
AUTHOR EMAIL: mruizo@fjd.es
CORRESP. AUTHOR/AFFIL: Ruiz-Ortega M.: Vascular and Renal Research Laboratory, Fundacion Jimenez Diaz, Universidad Autonoma Madrid, Avda. Reyes Catolicos, 2, 28040 Madrid, Spain
CORRESP. AUTHOR EMAIL: mruizo@fjd.es

Cardiovascular Research (Cardiovasc. Res.) (Netherlands) May 1, 2007, 74/2 (196-206)
CODEN: CVREA ISSN: 0008-6363
PUBLISHER ITEM IDENTIFIER: S0008636307000582
DOI: 10.1016/j.cardiores.2007.02.008
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 83

Transforming growth factor-beta (TGF-beta) participates in the pathogenesis of multiple cardiovascular diseases, including hypertension, restenosis, atherosclerosis, cardiac hypertrophy and heart failure. TGF-beta exerts pleiotropic effects on cardiovascular cells, regulating cell growth, fibrosis and inflammation. TGF-beta has long been believed to be the most important %%%extracellular%%% %%%matrix%%% regulator. We review the complex mechanisms involved in TGF-beta-mediated vascular fibrosis that includes the Smad signaling pathway, activation of protein kinases and crosstalk between these pathways. TGF-beta blockade diminishes fibrosis in experimental models, however better antifibrotic targets are needed for an effective therapy in human fibrotic diseases. A good candidate is connective tissue growth factor (CTGF), a downstream mediator of TGF-beta-induced fibrosis. Among the different factors involved in vascular fibrosis, Angiotensin II (AngII) has special interest. AngII can activate the Smad pathway independent of TGF-beta and shares with TGF-beta many intracellular signals implicated in fibrosis. Blockers of AngII have demonstrated beneficial effects on many cardiovascular diseases and are now one of the best options to block TGF-beta fibrotic responses. A better knowledge of the intracellular signals of TGF-beta can provide novel

therapeutic approaches for fibrotic diseases. (c) 2007 European Society of Cardiology.

2/7/52 (Item 6 from file: 72)
DIALOG(R)File 72:EMBASE
(c) 2008 Elsevier B.V. All rts. reserv.

0081600475 EMBASE No: 2007033774
The mineralized %%%extracellular%%% "%%%Matrix%%%" reloaded: A tissue engineering perspective
Sfeir C.
Department of Oral Medicine and Pathology, University of Pittsburgh, 3501 Terrace Street, 623 Salk Hall, Pittsburgh, PA 15261, United States
AUTHOR EMAIL: csfeir@pitt.edu
CORRESP. AUTHOR/AFFIL: Sfeir C.: University of Pittsburgh, Department of Oral Medicine and Pathology, 3501 Terrace Street, 623 Salk Hall, Pittsburgh, PA 15261, United States
CORRESP. AUTHOR EMAIL: csfeir@pitt.edu

Journal of Musculoskeletal Neuronal Interactions (J. Musculoskelet. Neuronal Interact.) (Greece) October 1, 2006, 6/4 (372-373)
CODEN: JMNIB ISSN: 1108-7161
DOCUMENT TYPE: Journal; Article RECORD TYPE: Citation
LANGUAGE: English
NUMBER OF REFERENCES: 15

2/7/53 (Item 7 from file: 72)
DIALOG(R)File 72:EMBASE
(c) 2008 Elsevier B.V. All rts. reserv.

0081267309 EMBASE No: 2006329591
Remodeling in asthma and chronic obstructive pulmonary disease
Postma D.S., Timens W.
Departments of Pulmonology and Pathology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; Department of Pulmonology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9731 GZ Groningen, Netherlands
AUTHOR EMAIL: d.s.postma@int.umcg.nl
CORRESP. AUTHOR/AFFIL: Postma D.S.: Department of Pulmonology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, 9731 GZ Groningen, Netherlands
CORRESP. AUTHOR EMAIL: d.s.postma@int.umcg.nl

Proceedings of the American Thoracic Society (Proc. Am. Thorac. Soc.) (United States) August 17, 2006, 3/5 (434-439)
ISSN: 1546-3222 eISSN: 1546-3222
DOI: 10.1513/pats.200601-006AW
URL: http://pats.atsjournals.org/cgi/reprint/3/5/434
DOCUMENT TYPE: Journal; Conference Paper RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 43

Airway and lung tissue remodeling and fibrosis play an important role in the development of symptoms associated with lung function loss in asthma and chronic obstructive pulmonary disease (COPD). In the past decades, much attention has been paid to the inflammatory cellular process involved in airway remodeling in these two diseases. However, it is increasingly clear that resident cells contribute to airway and lung tissue remodeling and to associated fibrosis as well. This article deals with some new aspects and discusses the role of vasculature and vascular endothelial growth factor in the development of airway obstruction and airway wall fibrosis in asthma and COPD. Moreover, it addresses the %%%extracellular%%% %%%matrix%%% (ECM) turnover as present in both asthma and COPD. All components of lung ECM (collagen, elastic fibers, proteoglycans) have been shown to be potentially altered in these two diseases. Finally, the interaction between transforming growth factor (TGF), Smad signaling, and TGF in the ECM turnover will be discussed. We propose that ECM damage and repair contribute to airway and lung tissue pathology and that the vasculature may enhance this process. The localization of this process is dependent on the etiology of the disease (i.e., allergen-driven in asthma and smoke-driven in COPD) and the local environment in which the pathologic process takes place.

2/7/54 (Item 8 from file: 72)
DIALOG(R)File 72:EMBASE
(c) 2008 Elsevier B.V. All rts. reserv.

0081251330 EMBASE No: 2006313596
Tumour microenvironment - TGFBeta: The molecular Jekyll and Hyde of cancer
Bierie B., Moses H.L.
Department of Cancer Biology, Vanderbilt University Medical Center, Nashville, TN 37232, United States
AUTHOR EMAIL: hal.moses@vanderbilt.edu
CORRESP. AUTHOR/AFFIL: Moses H.L.: Vanderbilt-Ingram Comprehensive Cancer Center, Vanderbilt University Medical Center, Nashville, TN 37232, United States
CORRESP. AUTHOR EMAIL: hal.moses@vanderbilt.edu

Nature Reviews Cancer (Nat. Rev. Cancer) (United Kingdom) July 1, 2006 6/7 (506-520)
CODEN: NRCAC ISSN: 1474-175X
PUBLISHER ITEM IDENTIFIER: N1926
DOI: 10.1038/nrc1926
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 157
Transforming growth factor-Beta (TGFBeta) signalling regulates cancer through mechanisms that function either within the tumour cell itself or through host-tumour cell interactions. Studies of tumour-cell-autonomous TGFBeta effects show clearly that TGFBeta signalling has a mechanistic role in tumour suppression and tumour promotion. In addition, factors in the tumour microenvironment, such as fibroblasts, immune cells and the %%%extracellular%%% %%%matrix%%%, influence the ability of TGFBeta to promote or suppress carcinoma progression and metastasis. The complex nature of TGFBeta signalling and crosstalk in the tumour microenvironment presents a unique challenge, and an opportunity to develop therapeutic intervention strategies for targeting cancer. (c) 2006 Nature Publishing Group.

2/7/55 (Item 9 from file: 72)
DIALOG(R)File 72:EMBASE
(c) 2008 Elsevier B.V. All rts. reserv.

0080134780 EMBASE No: 2004317928
TGF-beta-induced SMAD signaling and gene regulation: Consequences for %%%extracellular%%% %%%matrix%%% remodeling and wound healing
Schiller M., Javelaud D., Mauviel A.
INSERM U532, Institut de Recherche Sur la Peau, Univ. Paris VII, Hop. S.-Louis, 1 A., Paris, France
AUTHOR EMAIL: mauviel@chu-stlouis.fr
CORRESP. AUTHOR/AFFIL: Mauviel A.: INSERM U532, Institut de Recherche Sur la Peau, Univ. Paris VII, Hop. S.-Louis, 1 A., Paris, France
CORRESP. AUTHOR EMAIL: mauviel@chu-stlouis.fr

Journal of Dermatological Science (J. Dermatol. Sci.) (Ireland) August 1, 2004, 35/2 (83-92)
CODEN: JDSCE ISSN: 0923-1811
PUBLISHER ITEM IDENTIFIER: S0923181104000076
DOI: 10.1016/j.jdermsci.2003.12.006
DOCUMENT TYPE: Journal; Review RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 85

Members of the transforming growth factor-beta (TGF-beta) superfamily are pleiotropic cytokines that have the ability to regulate numerous cell

functions, including proliferation, differentiation, apoptosis, epithelial-mesenchymal transition, and production of %%%extracellular%%% %%%matrix%%%, allowing them to play an important role during embryonic development and for maintenance of tissue homeostasis. Three TGF-beta isoforms have been identified in mammals. They propagate their signal via a signal transduction network involving receptor serine/threonine kinases at the cell surface and their substrates, the SMAD proteins. Upon phosphorylation and oligomerization, the latter move into the nucleus to regulate transcription of target genes. This review will summarize recent advances in the understanding of the mechanisms underlying SMAD modulation of %%%extracellular%%% %%%matrix%%% gene expression in the context of wound healing and tissue fibrosis. (c) 2004 Japanese Society for Investigative Dermatology. Published by Elsevier Ireland Ltd. All rights reserved.

2/7/56 (Item 10 from file: 72)
DIALOG(R)File 72:EMBASE
(c) 2008 Elsevier B.V. All rts. reserv.

0079685106 EMBASE No: 2003394142
SPARC inhibits epithelial cell proliferation in part through stimulation of the transforming growth factor-beta-signaling system
Schiemann B.J.; Neil J.R.; Schiemann W.P.
Program in Cell Biology, Department of Pediatrics, Natl. Jewish Med. and Res. Center, Denver, CO 80206, United States
AUTHOR EMAIL: schiemannwp@njc.org
CORRESP. AUTHOR/AFFIL: Schiemann W.P.: Program in Cell Biology, Department of Pediatrics, Natl. Jewish Med. and Res. Center, Denver, CO 80206, United States
CORRESP. AUTHOR EMAIL: schiemannwp@njc.org

Molecular Biology of the Cell (Mol. Biol. Cell) (United States)
October 1, 2003, 14/10 (3977-3988)
CODEN: MBCEE ISSN: 1059-1524
DOI: 10.1091/mbc.E03-01-0001
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 45

Secreted protein, acidic and rich in cysteine (SPARC) is a multifunctional secreted protein that regulates cell-cell and cell-matrix interactions, leading to alterations in cell adhesion, motility, and proliferation. Although SPARC is expressed in epithelial cells, its ability to regulate epithelial cell growth remains largely unknown. We show herein that SPARC strongly inhibited DNA synthesis in transforming growth factor (TGF)-beta-sensitive Mv1Lu cells, whereas moderately inhibiting that in TGF-beta-insensitive Mv1Lu cells (i.e., R1B cells). Overexpression of dominant-negative Smad3 in Mv1Lu cells, which abrogated growth arrest by TGF-beta, also attenuated growth arrest stimulated by SPARC. Moreover, the extracellular calcium-binding domain of SPARC (i.e., SPARC-EC) was sufficient to inhibit Mv1Lu cell proliferation but not that of R1B cells. Similar to TGF-beta and thrombospondin-1, treatment of Mv1Lu cells with SPARC or SPARC-EC stimulated Smad2 phosphorylation and Smad2/3 nuclear translocation: the latter response to all agonists was abrogated in R1B cells or by pretreatment of Mv1Lu cells with neutralizing TGF-beta antibodies. SPARC also stimulated Smad2 phosphorylation in MB114 endothelial cells but had no effect on bone morphogenetic protein-regulated %%%Smad1%%% phosphorylation in either Mv1Lu or MB114 cells. Finally, SPARC and SPARC-EC stimulated TGF-beta-responsive reporter gene expression through a TGF-beta receptor- and Smad2/3-dependent pathway in Mv1Lu cells. Collectively, our findings identify a novel mechanism whereby SPARC inhibits epithelial cell proliferation by selectively commandeering the TGF-beta signaling system, doing so through coupling of SPARC-EC to a TGF-beta receptor- and Smad2/3-dependent pathway.

2/7/57 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
(c) 2008 American Chemical Society. All rts. reserv.

149315451 CA: 149(14)315451x PATENT
Medical devices comprising drug compositions and method for the treatment or prevention of spinal disorders
INVENTOR(AUTHOR): Diwan, Ashish; Diwan, Divya
LOCATION: Australia
ASSIGNEE: Cellixe Pty. Ltd.
PATENT: PCT International ; WO 2008101300 A1 DATE: 20080828
APPLICATION: WO 2008AU242 (20080222) *US 2007PV903131 (20070223) *US 2007PV12712 (20071210)
PAGES: 162pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
IPCR8 Level Value Position Status Version Action Source Office:
A61K-0038/18 A I F B 20060101 H AU
A61P-0019/00 A I L B 20060101 H AU
DESIGNATED COUNTRIES: AE; AG; AL; AM; AO; AT; AU; AZ; BA; BB; BG; BH; BR; BW; BY; BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DO; DZ; EC; EE; EG; ES; FI; GB; GD; GE; GH; GM; GT; HN; HR; HU; ID; IL; IN; IS; JP; KE; KG; KM; KN; KP; KR; KZ; LA; LC; LK; LR; LS; LT; LU; LY; MA; MD; ME; MG; MK; MN; MW; MX; MY; MZ; NA; NG; NI; NO; NZ; OM; PG; PH; PL; PT; RO; RS; RU; SC; SD; SE; SG; SK; SL; SM; SV; SY; TJ; TM; TN; TR; TT DESIGNATED REGIONAL: AT; BE; BG; CH ; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; HR; HU; IE; IS; IT; LT; LU; LV; MC; MT; NL; NO; PL; PT; RO; SE; SI; SK; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GQ; GW; ML; MR; NE; SN; TD; TG; BW; GH; GM; KE; LS; MW; MZ; NA; SD; SL; SZ; TZ; UG; ZM; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM
SECTION:
CA263001 Pharmaceuticals
CA201XXX Pharmacology
CA239XXX Biochemical Methods
CA214XXX Mammalian Pathological Biochemistry
IDENTIFIERS: spinal disorder intervertebral disk degeneration treatment drug GDF6
DESCRIPTORS:
Regeneration,animal...
disk; medical devices comprising drug comprs. and method for the treatment or prevention of spinal disorders
Viscosity...
drug; medical devices comprising drug comprs. and method for the treatment or prevention of spinal disorders
Extracellular matrix...
formation; medical devices comprising drug comprs. and method for the treatment or prevention of spinal disorders
Transcription factors...
gene MSX2; medical devices comprising drug comprs. and method for the treatment or prevention of spinal disorders
Spinal column...
intervertebral disk, degeneration; medical devices comprising drug comprs. and method for the treatment or prevention of spinal disorders
Spinal column,disease...
intervertebral disk hernia; medical devices comprising drug comprs. and method for the treatment or prevention of spinal disorders
Animal cell...
IVD (intervertebral disk); medical devices comprising drug comprs. and method for the treatment or prevention of spinal disorders
Adenoviral vectors... Cell differentiation... Cell migration... Cell proliferation... Drug delivery systems... Drug screening... Drugs... Gene therapy... Medical goods... Ovis aries... Pharmaceutical implants... Pharmaceutical injections... Proteins... Sheep... Signal transduction...
Spinal column,disease... Stem cell... Surgery...
medical devices comprising drug comprs. and method for the treatment or prevention of spinal disorders
Bone marrow...
mesenchymal stem cells; medical devices comprising drug comprs. and method for the treatment or prevention of spinal disorders
Gene,animal...
MSX-1; medical devices comprising drug comprs. and method for the treatment or prevention of spinal disorders
Gene,animal...
MSX-2; medical devices comprising drug comprs. and method for the treatment or prevention of spinal disorders
Transcription factors...

MSX1; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
Controlled-release drug delivery systems...
slow; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
Transcription factor Smad...
Smad1; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
Transcription factor Smad...
Smad4; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
Transcription factor Smad...
Smad5; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
Transcription factor Smad...
Smad8; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
Pain...
spinal; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
Medical goods...
stents; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
Collagens...
synthesis; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
Recombination,genetic...
translocation; 8q22.2 and 8q23.316, breakpoint; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
Bone morphogenetic protein receptors...
type IA; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
Bone morphogenetic protein receptors...
type IB; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
Bone morphogenetic protein receptors...
type II; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
CAS REGISTRY NUMBERS:
193830-09-0 medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
1050695-13-0 1050695-16-3 1050695-18-5 1050695-20-9 1050695-21-0 1050695-22-1 1050695-23-2 1050695-24-3 1050695-25-4 1050695-26-5 1050695-27-6 1050695-28-7 1050695-29-8 1050695-30-1 1050695-31-2 1050695-33-4 1050695-35-6 1050695-36-7 1050695-37-8 1050695-38-9 1050695-39-0 1050695-40-3 unclaimed nucleotide sequence; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
1050695-14-1 1050695-15-2 1050695-17-4 1050695-19-6 1050695-32-3 1050695-34-5 1050695-41-4 1050695-42-5 unclaimed protein sequence; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders
143413-47-2 253141-50-3 unclaimed sequence; medical devices comprising drug compns. and method for the treatment or prevention of spinal disorders

2/7/58 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

148577820 CA: 148(26)577820s JOURNAL
BMP4 induces an epithelial-mesenchymal transition-like response in adult airway epithelial cells
AUTHOR(S): Molloy, Emer L., Adams, Aine, Moore, J. Bernadette; Masterson, Joanne C., Madrigal-Estebas, Laura, Mahon, Bernard P.; O'Dea, Shirley
LOCATION: Institute of Immunology, Biology Department, National University of Ireland, Maynooth, Ire.,
JOURNAL: Growth Factors (Growth Factors) DATE: 2008 VOLUME: 26 NUMBER: 1 PAGES: 12-22 CODEN: GRFAEC ISSN: 0897-7194 LANGUAGE: English PUBLISHER: Informa Healthcare
SECTION:
CA202010 Mammalian Hormones
IDENTIFIERS: BMP4 epithelium mesenchyme transition adult airway signaling
DESCRIPTORS:
Collagens...
A1; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Catenins...
.beta.-; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Bone morphogenetic protein 4... Cell migration... Desmins...
Development,mammalian postnatal... Extracellular matrix... Fibroblast...
Fibronectins... Human... Phosphorylation,biological... Signal transduction ... Vimentins...
BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Epithelium...
bronchial; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Tenascins...
C; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
CD antigens...
CD106; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Bronchi... Respiratory system...
epithelium; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Lung,disease...
fibrosis; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Catenins...
.gamma.-; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Transcription factors...
gene twist; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Cell proliferation...
inhibition; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Inflammation... Lung,disease...
pneumonitis; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Fibrosis...
pulmonary; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Epithelium...
respiratory tract; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Transcription factor Smad...
Smad1; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Transcription factor Smad...
Smad5; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Transcription factor Smad...
Smad8; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Transcription factors...
Snai1; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Transcription factors...
Snai2; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Transcription factors...
Snai3; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof

Transforming growth factor beta....
TGF.beta.1, BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Collagens...
type I, A2; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Collagens...
type V, VA1, BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Collagens...
type VI, .alpha.1; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Cell adhesion molecules...
VCAM-1 (vascular cell adhesion mol. 1); BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Transcription factors...
Zeb1; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Transcription factors...
Zeb2; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Cell junction...
zonula adherens; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Cadherins...
1; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
Cadherins... Thrombospondins...
2; BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof
CAS REGISTRY NUMBERS:
109489-77-2 146480-35-5 182970-56-5 BMP4 induction of epithelial-mesenchymal transition-like response in adult airway epithelial cells and mechanisms thereof

2/7/59 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

147403226 CA: 147(19)403226x JOURNAL
Endothelial-to-mesenchymal transition contributes to cardiac fibrosis
AUTHOR(S): Zeisberg, Elisabeth M.; Tarnavski, Oleg; Zeisberg, Michael; Dorfman, Adam L.; McMullen, Julie R.; Gustafsson, Erika; Chandraker, Anil; Yuan, Xueli; Pu, William T.; Roberts, Anita B.; Neilson, Eric G.; Sayegh, Mohamed H.; Izumo, Seigo; Kalluri, Raghu
LOCATION: Beth Israel Deaconess Medical Center, Division of Matrix Biology, Department of Medicine, Harvard Medical School, Boston, MA, 02215, USA
JOURNAL: Nat. Med. (N. Y., NY, U. S.) (Nature Medicine (New York, NY, United States)) DATE: 2007 VOLUME: 13 NUMBER: 8 PAGES: 952-961 CODEN: NAMEFI ISSN: 1078-8956 LANGUAGE: English PUBLISHER: Nature Publishing Group
SECTION:
CA214005 Mammalian Pathological Biochemistry
IDENTIFIERS: heart fibrosis endothelium mesenchyme transition signaling BMP7 allograft rejection
DESCRIPTORS:
Bone morphogenetic protein receptors...
ALK2, systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Transplant rejection...
allotransplant; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Stem cell...
bone marrow-derived, systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Fibrosis...
cardiac; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Endothelium...
coronary arterial; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Artery...
coronary, endothelium; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Extracellular matrix...
endothelial-mesenchymal transition contributes to cardiac fibrosis
Endothelium... Mesenchyme...
endothelial-mesenchymal transition; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Heart,disease...
fibrosis; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Transplant and Transplantation...
heart; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Heart,disease...
left ventricle, diastolic dysfunction; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Transcription factor Smad...
Smad1; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Transcription factor Smad...
Smad2; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Transcription factor Smad...
Smad3; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Bone marrow...
stem cells; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Bone morphogenetic protein 7... Fibroblast... Fibronectins... Human... mRNA ... Signal transduction biological...
systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Transforming growth factor .beta....
TGF.beta.1; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Heart...
transplant; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Collagens...
type I; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Bone morphogenetic protein receptors...
type IA; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Bone morphogenetic protein receptors...
type II; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis
Collagens...
type III; systemic administration of recombinant human BMP-7 inhibited endothelial-mesenchymal transition and progression of cardiac fibrosis

2/7/60 (Item 4 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

144484914 CA: 144(26)484914c JOURNAL
BMP and FGF regulatory pathways control cell lineage diversification of heart valve precursor cells
AUTHOR(S): Lincoln, Joy, Alfieri, Christina M.; Yutzey, Katherine E.
LOCATION: Division of Molecular Cardiovascular Biology, Children's Hospital Medical Center, Cincinnati, OH, 45229, USA
JOURNAL: Dev. Biol. (San Diego, CA, U. S.) (Developmental Biology (San Diego, CA, United States)) DATE: 2006 VOLUME: 292 NUMBER: 2 PAGES: 290-302 CODEN: DEBIAO ISSN: 0012-1606 PUBLISHER ITEM IDENTIFIER: 0012-1606(05)00942-5 LANGUAGE: English PUBLISHER: Elsevier
SECTION:
CA212003 Nonmammalian Biochemistry
IDENTIFIERS: BMP FGF pathway cell diversification heart valve precursor, cartilage cell lineage differentiation heart valve BMP2 chicken embryo, tendon cell lineage differentiation heart valve FGF4 chicken embryo, aggrecan sox9 heart valve differentiation chick embryo BMP2, scleraxis tenascin heart valve differentiation chick embryo FGF4
DESCRIPTORS:
Bone morphogenetic proteins...
BMP and FGF control cartilage and tendon cell lineage differentiation during formation of heart valve leaflets and chordae tendineae in chicken embryo
Aggrecans...
BMP2 activates Smad1/5/8 phosphorylation and induces cartilage-assocd. sox9 and aggrecan expression during heart valve formation in chick embryos
Embryo,animal... Cell differentiation...
BMP2 and FGF4 control cartilage and tendon cell lineage differentiation during formation of heart valve leaflets and chordae tendineae in chicken embryo
Cartilage... Bone morphogenetic protein 2...
BMP2 regulates cartilage cell lineage differentiation from limb bud and somites of chick embryo during heart valve formation
Extracellular matrix...
extracellular matrix proteins and assocd. transcription factors are differentially localized in differentiating heart valve leaflets and chordae tendineae in chick embryo
Tenascins...
FGF4 increases phosphorylated MAPK signaling and promotes tendon-assocd. scleraxis and tenascin expression during heart valve formation in chick embryos
Tendon...
FGF4 regulates tendon cell lineage differentiation from limb bud and somites of chick embryo during heart valve formation
Transcription factors...
Scleraxis; FGF4 increases phosphorylated MAPK signaling and promotes tendon-assocd. scleraxis and tenascin expression during heart valve formation in chick embryos
Transcription factors...
Smad1/5/8; BMP2 activates Smad1/5/8 phosphorylation and induces cartilage-assocd. sox9 and aggrecan expression during heart valve formation in chick embryos
Transcription factors...
SOX9; BMP2 activates Smad1/5/8 phosphorylation and induces cartilage-assocd. sox9 and aggrecan expression during heart valve formation in chick embryos
Heart...
valve, BMP2 and FGF4 control cartilage and tendon cell lineage differentiation during formation of heart valve leaflets and chordae tendineae in chicken embryo
CAS REGISTRY NUMBERS:
62031-54-3 BMP and FGF control cartilage and tendon cell lineage differentiation during formation of heart valve leaflets and chordae tendineae in chicken embryo
142243-02-5 FGF4 increases phosphorylated MAPK signaling and promotes tendon-assocd. scleraxis and tenascin expression during heart valve formation in chick embryos
123584-45-2 FGF4 regulates tendon cell lineage differentiation from limb bud and somites of chick embryo during heart valve formation

2/7/61 (Item 5 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

143264185 CA: 143(15)264185e JOURNAL
Smad1 in diabetic nephropathy
AUTHOR(S): Matsubara, Takeshi
LOCATION: Department of Geriatric Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan, 606-8507
JOURNAL: Naibunpi, Tonyobyoka (Naibunpi, Tonyobyoka) DATE: 2005 VOLUME: 20 NUMBER: 3 PAGES: 236-242 CODEN: NATOFF ISSN: 1341-3724 LANGUAGE: Japanese PUBLISHER: Kagaku Hyoronsha
SECTION:
CA214000 Mammalian Pathological Biochemistry
IDENTIFIERS: review Smad1 collagen diabetic nephropathy glomerulosclerosis
DESCRIPTORS:
Kidney,disease... Inflammation...
diabetic glomerulonephritis; Smad1 in regulation of type IV collagen transcription and its role in diabetic nephropathy and glomerulosclerosis
Kidney,disease...
diabetic nephropathy; Smad1 in regulation of type IV collagen transcription and its role in diabetic nephropathy and glomerulosclerosis
Transcription factors...
Smad-1; Smad1 in regulation of type IV collagen transcription and its role in diabetic nephropathy and glomerulosclerosis
Transcriptional regulation... Human...
Smad1 in regulation of type IV collagen transcription and its role in diabetic nephropathy and glomerulosclerosis
Collagens,biological studies...
type IV; Smad1 in regulation of type IV collagen transcription and its role in diabetic nephropathy and glomerulosclerosis

2/7/62 (Item 6 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

131040180 CA: 131(4)40180p JOURNAL
Extracellular matrix-associated bone morphogenetic proteins are essential for differentiation of murine osteoblastic cells in vitro
AUTHOR(S): Suzawa, Miyuki; Takeuchi, Yasuhiro; Fukumoto, Seiji; Kato, Shigeaki; Ueno, Naoto; Miyazono, Kohei; Matsumoto, Toshio; Fujita, Toshiro
LOCATION: Fourth Department of Internal Medicine, University of Tokyo School of Medicine, Tokyo, Japan, 112
JOURNAL: Endocrinology DATE: 1999 VOLUME: 140 NUMBER: 5 PAGES: 2125-2133 CODEN: ENDOAO ISSN: 0013-7227 LANGUAGE: English PUBLISHER: Endocrine Society
SECTION:
CA202010 Mammalian Hormones
IDENTIFIERS: extracellular matrix bone morphogenetic protein osteoblast differentiation
DESCRIPTORS:
Bone formation... Bone morphogenetic proteins... Extracellular matrix...
Osteoblast... Signal transduction,biological...
extracellular matrix-assocd. bone morphogenetic proteins requirement for osteoblast differentiation and mechanisms thereof
Biological transport...
intracellular, Smad1 nuclear; extracellular matrix-assocd. bone morphogenetic proteins requirement for osteoblast differentiation and mechanisms thereof
Animal cell line...
MC3T3-E1; extracellular matrix-assocd. bone morphogenetic proteins requirement for osteoblast differentiation and mechanisms thereof
Mesenchyme...

osteoblast differentiation, extracellular matrix-assocd. bone morphogenetic proteins requirement for osteoblast differentiation and mechanisms thereof
Cell differentiation...
osteoblast; extracellular matrix-assocd. bone morphogenetic proteins requirement for osteoblast differentiation and mechanisms thereof
Cell nucleus...
Smad1 translocation, extracellular matrix-assocd. bone morphogenetic proteins requirement for osteoblast differentiation and mechanisms thereof
Transcription factors...
Smad1; extracellular matrix-assocd. bone morphogenetic proteins requirement for osteoblast differentiation and mechanisms thereof
Bone morphogenetic protein receptors...
type II; extracellular matrix-assocd. bone morphogenetic proteins requirement for osteoblast differentiation and mechanisms thereof
Bone morphogenetic proteins...
2; extracellular matrix-assocd. bone morphogenetic proteins requirement for osteoblast differentiation and mechanisms thereof
Bone morphogenetic proteins...
2B; extracellular matrix-assocd. bone morphogenetic proteins requirement for osteoblast differentiation and mechanisms thereof
10nov08 09:49:31 User219511 Session D743.4
$1.28 0.362 DialUnits File154
$6.96 29 Type(s) in Format 7
$6.96 29 Types
$8.24 Estimated cost File154
$0.58 0.165 DialUnits File155
$0.58 Estimated cost File155
$1.53 0.248 DialUnits File5
$24.40 10 Type(s) in Format 7
$24.40 10 Types
$25.93 Estimated cost File5
$1.43 0.142 DialUnits File71
$17.15 7 Type(s) in Format 7
$17.15 7 Types
$18.58 Estimated cost File71
$3.65 0.284 DialUnits File72
$35.50 10 Type(s) in Format 7
$35.50 10 Types
$39.15 Estimated cost File72
$2.24 0.174 DialUnits File73
$2.24 Estimated cost File73
$4.97 0.381 DialUnits File399
$17.88 6 Type(s) in Format 7
$17.88 6 Types
$22.85 Estimated cost File399
OneSearch, 7 files, 1.756 DialUnits FileOS
$0.26 TELNET
$117.83 Estimated cost this search
$122.74 Estimated total session cost 3.171 DialUnits
Logoff: level 05.22.00 D 09:49:31

Connection closed by remote host